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Formulation and Evaluation of Sustained Release Tablets Containing Atomoxetine Hydrochloride

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ABSTRACT:

The purpose of this research work was to establish sustained release tablets of Atomoxetine hydrochloride. The tablets were prepared by direct compression technique using HPMC-K4M, HPMC-K100M, Eudragit RSPO, Ethyl Cellulose as Sustained release polymer. These SR tablets were evaluated by different parameters such as weight variation, friability, assay, hardness, thickness, swelling index, in-vitro drug release study. The F9 formulation (containing HPMC K100M : EC)are optimized on the basis of in-vitro drug release studies.

KEYWORDS: Sustained release tablets, Atomoxetine hydrochloride

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INTRODUCTION:

Conventional routes of drug administration such as oral, intramuscular, intravenous have been supplanted by the advent of new, novel drug delivery systems. In the pharmaceutical dosage forms several approaches are available to include the loading dose of a drug to the maintenance dose of a drug for sustained action.[1,2.3] Aatomoxetine HCl is a potent inhibitor of the presynaptic norepinephrine transporter with minimal affinity for other monoamine transporters or receptors and is the first non-stimulant medication approved for the management of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents and adults[4]. Atomoxetine HCl is well absorbed after oral administration with peak plasma concentration in 1 to 2 hours after a dose. Bioavailability is about 63% in extensive metabolisers. The half life of drug is 5 hr in extensive metabolisers[4]. The log P value of the drug is 3.95 which is sufficient to cross the oral mucosa. It has low therapeutic dose (10-100mg) and short half life. ADHD being a chronic disorder requires a continuous and long term treatment. Also the drug concentration at the site of action needs to be maintained constant to avoid the mood swings experienced by the patient. By considering above points, this drug is an ideal candidate for design and development of sustained drug delivery systems[5,6,7].

Materials and methods:

Atomoxetine hydrochloride (99.85% purity), was gift sample from Torrent Pharmaceuticals, Methocel K100M, K4M, Ethyl cellulose (Colorcon Asia Pvt ltd, Goa, India), Eudragit RSPO(Evonik, India),Magnesium Stearate, Talc (Astron Chemicals, Ahmedabad, India), all other reagents and chemicals used were of analytical reagent grade.

Preparation of Sustained release tablets

The tablets were prepared by direct compression technique involving one single step and composition of all batches is shown into the Table No. 1.

Step1[9]

The API and polymer mixture was mixed homogenously in a motor for 15 minutes. The mixture (200 mg) was then compressed using 8×32 round shaped flat punches on multi station tablet machine.

Formulation Design:[10]

The total dose of Atomoxetine HCl for once daily-sustained release formulation was calculated by the following equation, using available pharmacokinetic data.

$Css = F \times D / Cl \times \tau$

Where, F = Fraction of bioavailability
D = Conventional dose of tablets (mg)
Cl = Clearance (L/hr)

τ = time up to which tablet is required to be sustained (hr)

Loading dose = $Css \times V_d / F$

Where, V_d = Volume of distribution (L)
F = Fraction of bioavailability

Maintanance dose = $Css \times Cl \times \tau / F$

Total dose = L.D + M.D

Total dose for Atomoxetine HCl is 80 mg.

Table 1: The composition of SR tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Atomoxetine HCl	91.42	91.42	91.42	91.42	91.42	91.42	91.42	91.42	91.42	91.42	91.42	91.42
HPMC K4M	20	60	-	-	-		-	-	-	-	-	-
HPMC K100M	-	-	30	70	-	-	-	-	50	24	50	24
Ethyl cellulose	-	-	-	-	20	40	-	-	24	50	-	-
Eudragit RSPO	-	-	-	-	-	-	20	40	-	-	24	50
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
Lactose	72.58	32.58	62.58	22.58	72.58	52.58	72.58	52.58	18.58	18.58	18.58	18.58
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2
TOTAL	200	200	200	200	200	200	200	200	200	200	200	200

* Atomoxetine HCl is equivalent to 80 mg of Atomoxetine. All the quantities are given in mg.

EVALUATION PARAMETERS:

Pre compression parameters:

Angle of repose11 (θ):

The data obtained from angle of repose for all the formulations were found to be in the range of 29.460 and 36.700. All the prepared formulations showed the angle of repose less than 370, which reveals moderate flow property.

Densities12:

Loose bulk density (LBD) and tapped bulk density (TBD) for the blend was performed. The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.41 gm/ml to 0.55 gm/ml and 0.555 gm/ml to 0.588 gm/ml respectively.

Carr's index13:

The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 4.181 % to 29.43 %.

Hausner's ratio14:

Hausner's ratio of entire formulation showed between 1.04 and 1.24 indicates good flow properties.

Pre compression parameters of all batches has been shown into the Table No. 2.

POST COMPRESSION EVALUATION PARAMETERS:

Hardness[15]:

The hardness of all the prepared tablets was maintained within the 6 kg/cm^2 to 8 kg/cm^2. The mean hardness test results are shown in table no. 3.

Thickness[16]:

The mean thickness was (n=3) almost uniform in all the formulations and value is 3 mm. The standard deviation values indicated that all the formulations were within the range. The results of thickness for tablets were shown in Table no. 3

Average weight[16]:

The average weight was found in all designed formulations in the range of 196 to 206 mg. The mean weight variation test results are shown in Table no.3

Friability test[16]:

The friability was found in all designed formulations in the range 0.4 to 0.53 % to be well within the approved range (<1%).The friability study results were tabulated in Table no.3

Table 2: Pre Compression Evaluation Parameters

Formulation Code	Parameters				
	Bulk Density (gm/ml) ± SD, n=3	**Tapped Density (gm/ml) ± SD, n=3**	**Angle of Repose (θ) ± SD, n=3**	**Carr's Index (%) ± SD, n=3**	**Hausner's Ratio ± SD, n=3**
F1	0.5	0.555	33.66	9.909	1.11
F2	0.45	0.555	36.12	18.918	1.23
F3	0.5	0.574	33.63	12.891	1.14
F4	0.45	0.555	28.91	18.918	1.23
F5	0.55	0.574	33.68	4.181	1.04
F6	0.5	0.561	29.46	10.873	1.12
F7	0.5	0.549	31.32	9.8	1.09
F8	0.5	0.568	36.46	13.62	1.13
F9	0.55	0.588	33.02	6.46	1.06
F10	0.45	0.561	30	19.78	1.24
F11	0.5	0.568	36.70	11.97	1.13
F12	0.41	0.581	34.2	29.43	1.41

Drug Content[16]:

The drug content uniformity was performed for all the formulations and results are tabulated in Table no. 3. Three trials from each batch were analyzed spectrophotometrically. The average value and standard deviations of all the formulations were calculated. The percentage drugs content of the tablets were found to be between 86.33 to 96.33 % of Atomoxetine HCL. The results were within the range and that indicated uniformity of mixing.

In Vitro Drug Release[16,17,18,19,20]

The United States Pharmacopeia (USP) type II paddle method was used to study the drug release for SR tablets. The dissolution medium consisted of 900 mL of 0.1 N HCl for 2 hours and 900 mL of phosphate buffer pH 6.8 for remaining hours. The release was performed at 37^{o}C ± 0.5^{o}C, with a rotation speed of 50 rpm. The Samples (5 mL) were withdrawn at 1,2,3,4,5,6,7,8,12,14,24 hrs time intervals and replaced with fresh medium[17].The samples were filtered through 0.2-μm Whatman filter paper and analyzed by UV spectrophotometry at 267 nm[18]. Table No. 4 shows the n vitro drug release for all the formulation.

Table 3: Post Compression Evaluation Parameters

Formulation Code	Parameter				
	Hardness (kg/cm^2) ± SD, n=3	Thickness (mm) ± SD, n=3	Average weight(mg) ± SD, n=3	Friability (%) ± SD, n=3	Drug Content (%) ± SD, n=3
F1	6	3	198	0.5	91.42
F2	7	3	204	0.43	94
F3	6	3	197	0.4	86.33
F4	6	3	202	0.6	89.65
F5	8	3	198	0.41	94.43
F6	8	3	196	0.46	86.33
F7	7	3	200	0.51	96.33
F8	7	3	202	0.43	89.21
F9	8	3	206	0.52	95.21
F10	8	3	202	0.46	86.80
F11	8	3	202	0.6	96.33
F12	7	3	196	0.53	92.54

Formulation code	Time (hr)	% CDR
F1	12	98.76
F2	12	90.01
F3	24	101.02
F4	24	92.07
F5	6	100.19
F6	14	98.89
F7	8	98.08
F8	14	99.86
F9	24	98.23
F10	24	94.50
F11	24	97.23
F12	24	98.41

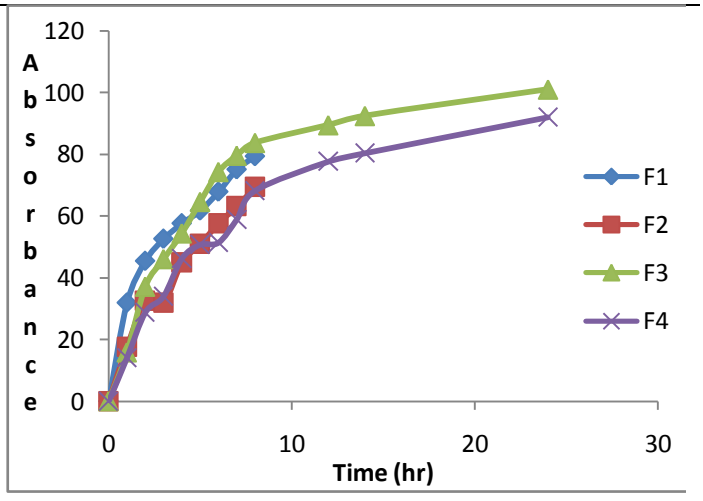

Fig 1.1 In Vitro releae study of F1 to F4

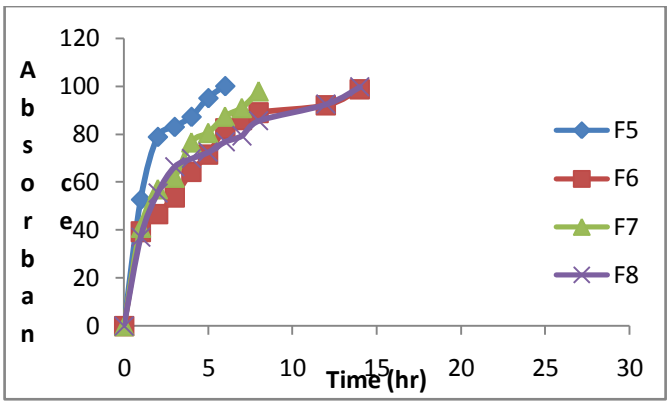

Fig 1.2 In Vitro releae study of F5 to F8

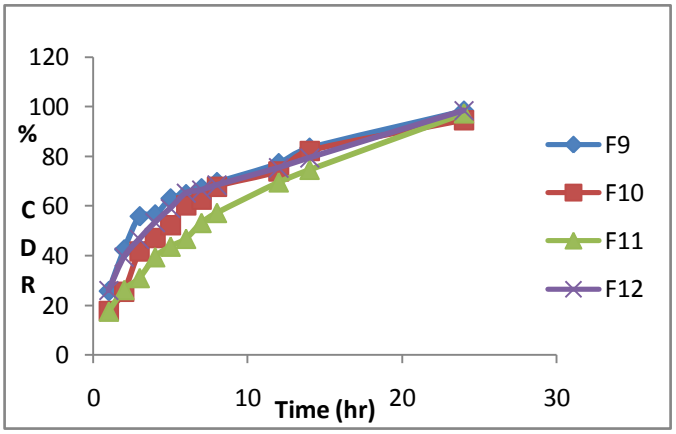

Fig 1.3 In Vitro releae study of F9 to F12

RESULTS AND DISCUSSION:

Atomoxetine HCl is first non stimulant agent in category of antipsychotic. Attention Deficit Hyperactivity Disorder is a disease which require a long term treatment. So, sustained release tablet of atomoxetine HCl is prepared to fullfil the disease condition. All batches are prepared by direct compression technique. HPMC K4M (F1 & F2) alone is not capable to achieve sustained release up to 24 hrs. So higher grade HPMC polymer is used. HPMC K100 M (F3 & F4) is capable of sustaining release up to 24 hrs and it follows the proper release rate for the loading dose but in case of maintenance dose it give faster drug release. Similarly EC (F5 & F6) alone is not that much effective as compare to combination with HPMC K100M. Eudragit RSPO (F7 & F8) alone is more effective to attain sustain release as compare to EC. So, the combination of two different polymers has taken.(Hydrophilic and Hydrophobic). But in case of combination HPMC K100M + EC (F9 & F10) is more effective than HPMC + EUDRAGIT RSPO (F11 & F12) in achieving loading dose.

CONCLUSION:

To achieve the sustain release up to 24 hrs, combination of

HPMC K100M and EC (F9) is effective for gaining more better result as compare to single polymer.

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