Journal of Pharma Research
Available online through
www.jprinfo.com

Research Article
ISSN: 2319-5622

FORMULATION AND EVALUATION OF EXTENDED RELEASE ATOMOXETINE HYDROCHLORIDE MATRIX TABLET

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Received on: 04-07-2016; Revised and Accepted on: 18-07-2016

ABSTRACT

The present study was undertaken with an aim to formulate, develop & evaluate extended release tablet of an antidepressant drug, Atomoxetine hydrochloride which release drug in a controlled manner for a period of 24h. Two different polymer Karaya Gum & Metolose 90SH-4000SR were used at different ratios for the preparation of tablet. The tablet were prepared by Wet granulation method & evaluated for thickness, hardness, weight variation, friability, swelling index & in-vitro drug release. Formulation F_9 with combination of Karaya Gum & Metolose 90SH-4000SR was considered as an optimized formulation. The optimized formulation showed satisfactory extended drug release & remained on the surface of the medium for 24h & its release profile was comparable with the marketed formulation (AXEPTA). It can also be concluded that extended release tablet of Atomoxetine hydrochloride can be successfully formulated as an approach to reduce the frequency of administration & patient compliance.

Key Words: *Atomoxetine hydrochloride, Extended release tablet, Karaya gum, Metolose.*

INTRODUCTION

Oral route is the most oldest and convenient route for administration of therapeutic agents because of low cost of therapy and ease of administration lead to higher level of patient compliance. This route of drug administration have wide acceptance up to 50-60% of total dosage forms. The most popular solid dosage form is being tablets and capsules [1].

Extended release dosage form is designed in such a manner as to allow the enclosed drug available over an extended period of time after its administration. Extended drug delivery systems are beneficial especially for those patients who are not able to take medicine frequently specially in geriatric and mental patients. Extended release dosing can reduce peak-related side effect, maintain therapeutic plasma concentration between doses, and enables a less frequent dosing regimen. The rate of the drug release from solid dosage form may be modified by the technologies, which in general are based on modifying drug dissolution by controlling access of biological fluids to the drug through the use of barrier coating and controlling drug diffusion rates from dosage form [1, 2] .

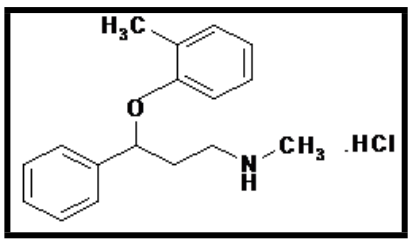

Fig. 1: Structure of Atomoxetine hydrochloride

Atomoxetine (ATMX) is a drug approved for the treatment of attention-deficit hyperactivity disorder (ADHD). It is sold in the form of hydrochloride salt of the Atomoxetine. It is a selective norepinephrine reuptake inhibitor (NRI). Atomoxetine is designated chemically as (-)-N-methyl-3-phenyl-3- (o-tolyloxy)-propylamine hydrochloride. The biological half life of Atomoxetine hydrochloride is 5 hours. So conventional Atomoxetine hydrochloride should be administered 2-3 times a day to maintain the therapeutic effect of the drug throughout the day. Atomoxetine hydrochloride extended release tablet reduces the dosage frequency and enhance patient compliance. A total of 9 formulations were developed using the variation proportions of Karaya Gum and Metolose 900SH-40SR as release retardant polymer by using wet granulation method [4].

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MATERIAL & METHOD

Materials:

Atomoxetine hydrochloride was obtained from ZCL chemicals Ltd., Mumbai. Karaya Gum was procured from Modern Science Lab. Nashik & Metolose 900SH-40SR and Luzenac pharma Talc was obtained from Signet Chemical Corporation Pvt.Ltd., Mumbai. Polyvinyl alcohol, Polyvinylpyrolidone, Magnesium Stearate was procured from Modern Science lab. Nashik. All other chemicals and reagents used were of analytical grades.

Method:

Formulation of Atomoxetine Hydrochloride Extended Release Tablets:

Atomoxetine hydrochloride Extended Release tablets were prepared by Wet granulation method. Accurately weighed Atomoxetine hydrochloride, Karaya Gum, Metolose900SH-40SR, lactose, mannitol were sifted using #60 and placed in separate poly bag. The sifted material were mixed for 5 min and granulated with the required quantity of Isopropyl alcohol as binder by kneading method (Hand granulation). The granules were passed through sieve and dried at room temperature, until the required moisture content is obtained (NMT 1-2%). Then the granules are size reduced, using sieve #20. Then the granules were finally lubricated using magnesium stearate after sifting it through #60, for 5 min. The lubricated granules were compressed into tablet each containing 40 mg Atomoxetine hydrochloride and a total weight of 110mg using 6mm Round FFBE punches. The formulation of the Atomoxetine hydrochloride extended release tablets are given in table no. 1

Precompression Parameters: [5, 7]

The granules were evaluated for Angle of repose, Bulk density, Tapeed density, Compressibility index, and Hausner's ratio. The Angle of repose was determined by Fixed funnel method to assess the flow property of granules. Bulk and Tapped Density were

determined using digital bulk density apparatus. Bulk density is the ratio between given mass of granules and its bulk volume. Tapped Density is the ratio between a given mass of granules and the constant/ fixed volume of tapped granules. The compressibility index and Hausner's ratio were determined by using Bulk and Tapped density of granules.

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

$$\text{Carr's Compressibility Index} = \frac{\text{TBD - LBD}}{\text{TBD}} \times 100$$

Where, TBD- Total bulk density
LBD- Loose bulk density

Postcompression Parameters: [5]

The prepared ER matrix tablets were evaluated for their hardness, weight variation, thickness and friability.

In vitro drug release studies:

The *in vitro* dissolution studies were carried out using USP dissolution apparatus type II at 50 rpm. Dissolution test was carried out for first two hour using 900ml of 0.1 N HCl & then remaining time in phosphate buffer of pH 6.8. The studies were performed at a temperature of 37˚C±0.5˚C. Analysis for Atomoxetine hydrochloride was done by by using double beam U.V spectrophotometer at 270nm. The *invitro* release of marketed product was carried out in similar manner.

Stability Study: [10]

The optimized formulation Atomoxetine Hydrochloride extended release tablets containing 40 mg drug were kept in bottles and stored at 25˚C- 60% RH and 40˚ C - 75% RH. Tablets were analyzed after three month for physical parameter and thickness, hardness, friability, %drug content.

RESULT AND DISCUSSION

The micromeritic studies were conducted and the Angle of repose was found in the range of 26.85 to 30.67 for all formulations. The Bulk Density and Tapped Density were found in the range 0.255to 0.414 and 0.274 to 0.453 respectively. The compressibility index ranged from 6.42 to 10.0. It proves that the flow behavior & compressibility of granules are good. All formulations showed excellent flowabillity as expressed in terms of micromeritic parameter in table no. 2.

The Thickness of tablet was found in the range of 3.80±0.01 to3.81±0.02mm. The result showed that the thickness of all formulated batches of tablets is found to be uniform. The hardness of all tablet formulation was found to be in the range of 4.5±0.03 to 5.0±0.01 kg/cm^2. It indicates that all the tablets have adequate mechanical strength.

The accepted percentage deviation was ±5 % for not more than 250 mg tablets. The results showed that weight variation was ranging from 109.18±0.02 to 110.06±0.05mg. Hence the tablet complies within the IP limits in the range of uniformity of weight.

In Friability test the maximum weight loss should not be more than 1%. The results revealed that the tablets passed the friability test. Drug content in different formulation was estimated by UV spectrophotometric method. The drug content was found in the range of 97.25±0.86 to 99.96±0.64. This indicates the drug was distributed almost uniformly throughout in the formulation in table no. 3.

The *in-vitro* release of Atomoxetine hydrochloride was slow and extended over a longer period of time (Fig. 2). The optimized formulation F_9 showed drug release up to 24 hours. The F_9 formulation compared with marketed sustained release tablet, the ER tablet showed excellent drug release profile (Fig. 3).

Stability study data of formulation F_9 reveals that there was no change in drug content, friability, λmax, etc. at 40˚Cwith 75% RH during the period of 90 days (Table no. 5).

Table No. 1: Formulation of Extended Release Atomoxetine hydrochloride matrix tablet using wet granulation method

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Atomoxetine hydrochloride	40	40	40	40	40	40	40	40	40
Karaya Gum	05	10	20	-	-	-	30	-	20
Metolose	-	-	-	05	10	20	-	30	20
Lactose	40	35	35	50	55	45	35	35	25
Mannitol	20	20	10	10	-	-	-	-	-
PVP-K-90 (10%solution)	10%	10%	10%	10%	10%	10%	10%	10%	10%
Talc	3	3	3	3	3	3	3	3	3
Magnesium Stearate	2	2	2	2	2	2	2	2	2

(All ingredients taken in mg per tablet)

Precompression Parameter:

Table No. 2: Micromeritic properties of Granules of Atomoxetine hydrochloride extended release formulation

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Angle of Repose (Θ)
F_1	0.304±0.002	0.327±0.001	9.27	28.34
F_2	0.294±0.001	0.318±0.008	7.54	26.85
F_3	0.255±0.004	0.274±0.023	6.56	28.03
F_4	0.331±0.002	0.345±0.052	9.27	30.13
F_5	0.414±0.002	0.453±0.006	10.0	30.67
F_6	0.304±0.003	0.340±0.001	10.0	27.52
F_7	0.273±0.002	0.302±0.045	6.74	28.69
F_8	0.255±0.004	0.274±0.007	6.56	29.35
F_9	0.304±0.007	0.326±0.002	6.42	29.37

Postcompression Parameter:

Table No. 3: Post- compression parameter of Atomoxetine hydrochloride extended release tablets

Formulation Code	Thickness (mm) Mean ± S.D.	Weight variation test (mg) (n=10) Mean ± S.D.	Hardness (Kg/cm^2) Mean ± S.D. (n=10)	Friability (%) (n=10)	Drug Content
F_1	3.80 ± 0.01	110.02 ± 0.002	4.6 ± 0.03	0.255	99.86 ± 0.89
F_2	3.81 ± 0.01	110.03 ± 0.032	4.6 ± 0.02	0.187	99.96 ± 0.64
F_3	3.81 ± 0.02	110.1 ± 0.05	4.8 ± 0.02	0.275	98.23 ± 0.35
F_4	3.80 ± 0.01	110.06 ± 0.05	4.7 ± 0.01	0.321	97.25 ± 0.86

F_5	3.80 ± 0.01	110.21 ± 0.03	4.5 ± 0.03	0.148	98.27 ± 0.32
F_6	3.80 ± 0.02	109.18 ± 0.02	4.9 ± 0.01	0.254	99.21 ± 0.35
F_7	3.80 ± 0.01	110.03 ± 0.021	5.0 ± 0.01	0.184	98.28 ± 0.54
F_8	3.81±0.01	110.3±0.01	4.8±0.04	0.335	98.66 ± 0.65
F_9	3.80±0.01	110.1±0.02	5.0±0.01	0.288	99.54 ± 0.38

Table No. 4: Drug release Kinetics from Atomoxetine hydrochloride [9]

Formulation code	Correlation Coefficient (r^2)				Release exponent (n)
	Zero order	First order	Higuchi	Peppas	
F_1	0.9426	0.9570	0.9865	0.9975	0.6030
F_2	0.8296	0.9786	0.9921	0.9928	0.5408
F_3	0.8898	0.9550	0.9971	0.9971	0.5687
F_4	0.8787	0.9652	0.9938	0.9958	0.5806
F_5	0.9083	0.9431	0.9960	0.9982	0.5422
F_6	0.9525	0.9227	0.9867	0.9974	0.6207
F_7	0.9068	0.9431	0.9952	0.9983	0.5469
F_8	0.8640	0.9798	0.9947	0.9946	0.5659
F_9	0.9546	0.9468	0.9875	0.9986	0.6236

Table No. 5: Stability studies of optimized formulation (F_9)

Parameter	Initial	1st month		2nd month		3rd month	
		RT	40°C	RT	40°C	RT	40°C
Appearance	Brownish white colour	Brownish white colour	Brownish white colour	Brownish white colour	Brownish white colour	Brownish white colour	Brownish white colour
Thickness (mm)	3.80	3.80	3.80	3.80	3.80	3.80	3.80
Weight variation (mm)	110.1±0.2	110.09± 0.19	110.09± 0.09	110.01± 0.08	110.1± 0.1	110.1±0.1	110.1± 0.1
Hardness (kg/cm²)	5± 0.01	5±0.01	5±0.01	5±0.01	5±0.01	5±0.01	5±0.01
λmax (nm)	270nm	270nm	270nm	270nm	270nm	270nm	270nm
Frability (%)	0.288	0.275	0.284	0.293	0.287	0.281	0.290
Drug content (%)	99.54 ± 0.38	99.74± 0.14	99.37± 0.54	99.82± 0.78	99.76 ± 0.32	99.23 ± 0.42	99.54± 0.38

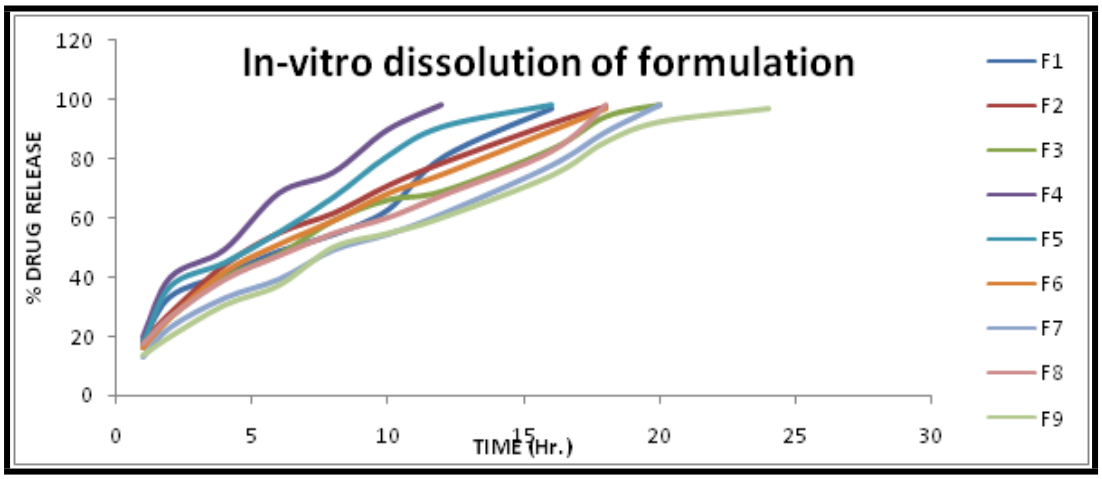

Fig. 2: Dissolution profile of formulation (F_1 - F_9)

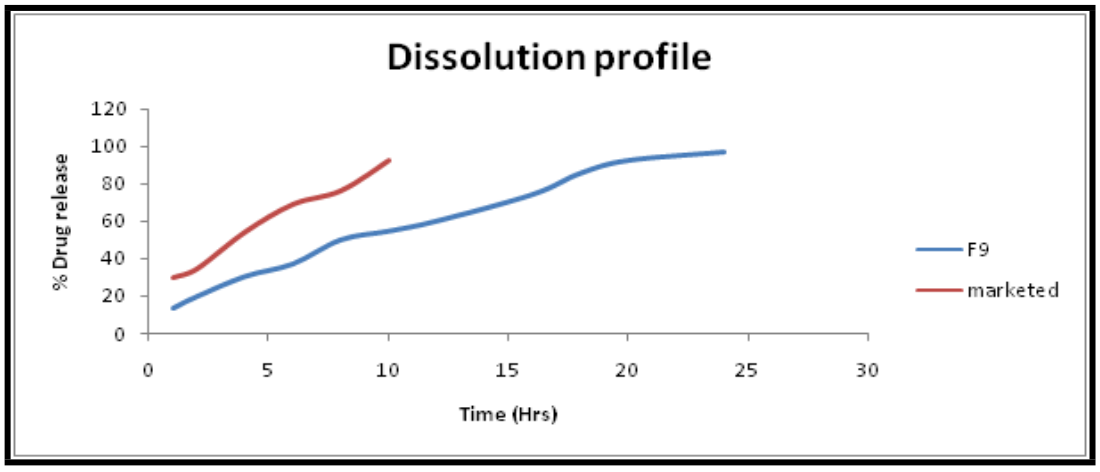

Fig. 3: Dissolution profile of formulation F_9 & Marketed formulation

CONCLUSION

It may be concluded that the Atomoxetine hydrochloride extended release tablet has been successfully formulated with good drug release profile for a prolonged period of time up to 24 hrs. It decrease the frequency of dose administration, prevents hyperactivity and attention deficiency & improve patient compliance.

ACKNOWLEDGEMENT

I would like to thank S.M.B.T COP, ZCL Chemicals, Mumbai, Signet chemicals, Mumbai.
My colleague,teachers, non-teaching staff and my beloved family.

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How to cite this article:

Supriya T. Garud et al., FORMULATION AND EVALUATION OF EXTENDED RELEASE ATOMOXETINE HYDROCHLORIDE MATRIX TABLET, J. Pharm. Res., 2016; 5(7): 164-167.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil