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Research Article

Designing and Assessing of Atomoxetine Matrix Tablets Using *Datura stramonium* Leave Mucilage for the Treatment of Attention-Deficit Hyperactivity Disorder.

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ABSTRACT
The authors aimed to extend discharge of Atomoxetine (ATX) tablets with a combination of herbal and synthetic polymers. ATX matrix tablets made with the blend of *Datura stramonium* leaves mucilage (DSLM) and Hydroxy Propyl Methyl Cellulose. The blend was assessed for flow possessions and the designed tablets were categorized for official and non official tests including ATX discharge. The ATX matrix tablets possess good ATX content with possible pre and post formulation parameters. The study concludes that there were no any chemical interactions between ATX with polymers used and DSLM can be a good polymer in grouping with other polymers for prolonged drug discharge.

KEYWORD
Atomoxetine, *Datura stramonium*, mucilage, matrix.

1. INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a cerebral complaint of the neuro developmental type. It is described by trouble in for feiting attention, extreme activity and acting deprived of esteems to significances, which are else not fitting for a person's age[1].

Atomoxetine (ATX) is a non-stimulant, choosy noradrenergic reuptake inhibitor, recommended in the dealing of ADHD in patients. After single oral dose, ATX extents extreme plasma levels ~1.5 h of admin and good drug for the present study [2].

Extended drug delivery systems with controlled ATX discharge can be realized by various techniques among them matrix system is a simple, inexpensive and effective [3, 4]. The use of costly polymers can be discharged by economical and easily available herbal leave mucilage from *Datura stramonium* leaves mucilage (DSLM).

2. MATERIALS AND METHODS

2.1. Material

The materials required in this work are illustrated in table 1.

Table 1: List of materials

Materials	Suppliers/Manufacturer
Atomoxetine	Gift sample by Intas Pharmaceuticals, Bangalore
HPMC	Fischer Chemic Ltd, Hyderabad
Lactose	Fischer Chemic Ltd, Hyderabad
Magnesium stearate	Fischer Chemic Ltd, Hyderabad
Talc	Fischer Chemic Ltd, Hyderabad
Water	Distillation unit of our Lab

2.2. Methods

2.2.1. Identification of Atomoxetine

Identification of ATX was scrutinized for a physical look, melting point and solubility.

2.2.2. Atomoxetine calibration curve

The procedure for plotting ATX calibration curve [5, 6] was illustrated in chart 1.

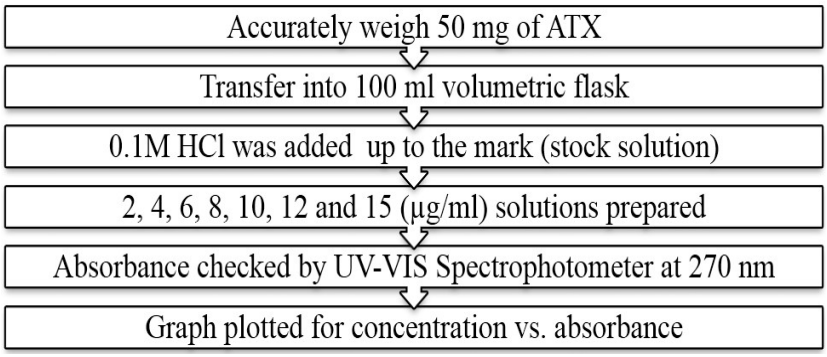

Chart 1. Procedure for obtaining Atomoxetine calibration curve.

2.2.3. Extraction of mucilage

The extraction and purification were done as styled by Ahad et al [7]. The fresh *Datura stramonium* leaves were washed, soaked and boiled in water. Later filtered isolated with Acetone, dried, # 80 sieved.

2.3. Drug excipient compatibility studies

2.3.1. Differential scanning calorimetry (DSC)

The DSC analyses of ATX and blend were done with Perkin Elmer, FTIR spectrophotometer to check any drug-excipient interaction. Each sample was placed in an aluminium pan separately with heating rates of 10°C/min from 50-300°C under nitrogen 50 ml/min.

2.3.2. FTIR study

FTIR spectra and distinctive peaks of ATX and ATX with excipient blend were made by Bruker IR spectrophotometer.

2.4. Calibration curve

ATX calibration curve shows a slope of 0.0836x-0.0115 with a regression (R^2) value of 0.9990 (Fig 1.).

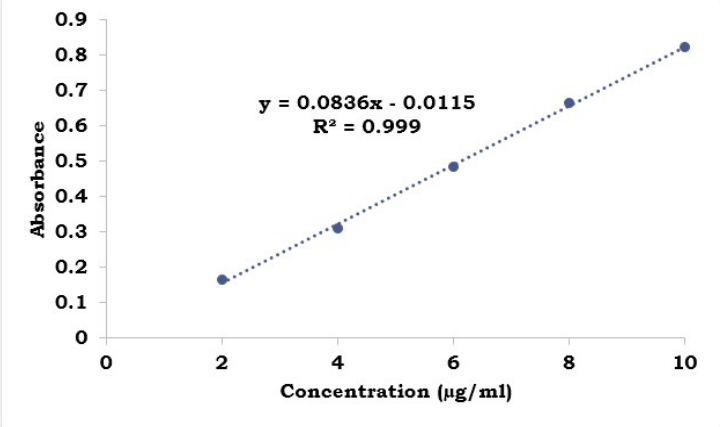

Fig.1. Calibration curve of Atomoxetine.

2.5. Formulation of tablets by wet granulation technique

Steps involved in the preparation [8] of sustained release tablets (SRT) shown chart 2.

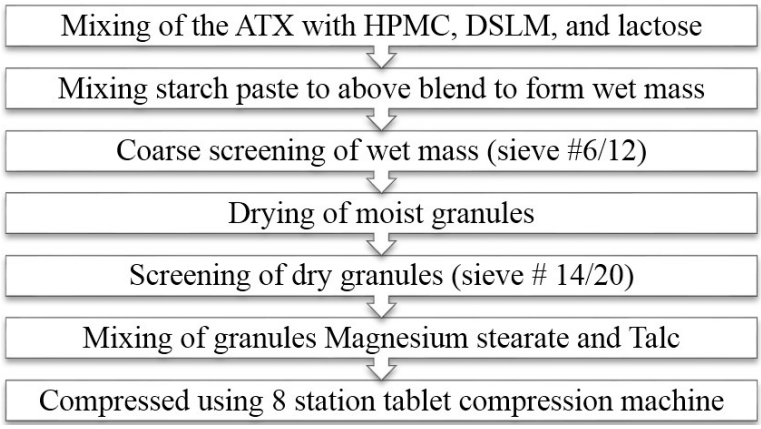

Chart 2. Steps involved in matrix tablet preparation.

2.6. Pre formulation studies

The dried granules were subjected to flow patterns for checking their easy movement from hopper to tablet dyes for compression [9, 10].

2.7. Post formulation studies

The prepared tablets were characterized for the following parameters [11, 12, 13].

2.7.1. Thickness of tablets

A sliding calliper was used to know the thickness of 5 tablets from each batch.

2.7.2. Uniformity of weight

20 tablets from each batch were weighed solely and mean weight was also resolute. Later the unorthodoxy of individual weights was calculated.

2.7.3. Tablet hardness

5 tablets were randomly taken from each batch and hardness was dogged by using Pfizer tester.

2.7.4. The loss on friability

A pre-weighed 10 tablets from each batch were allowed for 100 falls (4 min) from 6 inches and weighed after aspirating.

2.7.5. Determination of drug content in tablets

ATX content in the SRT was dogged by the procedure [14] explained in chart 3.

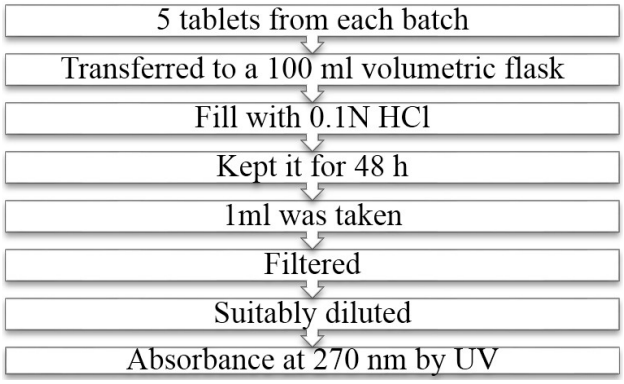

Chart 3. Procedure for determining the drug content in prepared tablets.

2.7.6. In vitro dissolution studies

The dissolution conditions adopted for drug dissolution [15] was concise in table 2.

Table 2. *In vitro* dissolution conditions.

Parameter	Description
Apparatus	USP-II
Rotation (rpm)	100
Medium	0.1 M HCl for first 2 h then in pH 6.8 phosphate buffer solution for 10 h
Volume	900 ml
Temperature	37±0.5°C

Sampling at	1, 4, 6, 8, 10 and 12 h
Wavelength	270 nm

3. RESULTS AND DISCUSSION

3.1. Results API characterization

ATX appearance, melting point, and solubility were listed in chart 4 which indicates the purity of the sample.

Chart 4. Atomoxetine identification parameters.

3.2. Compatibility studies

Neither loss of precise peaks nor productions of new peaks were seen in the DSC of ATX thermogram when equated to pure ATX which signposts no incompatibility of ATX with polymers used (table 3).

Table 3. DSC thermograms of drug and polymers used.

DSC sample	**Endothermic events (°C)**			**ΔH Fusion**	**Inference**
	T onset	**T peak**	**T end**	**Enthalpy (J)**	
Atomoxetine	158.08	132.84	135.15	-288.45	An endothermic peak
Atomoxetine+ Polymers	151.44	131.11	133.85	-255.19	A shift in peak to left due to positive blending of Atomoxetine with polymers

The FTIR spectra expressed that the typical bands of ATX were not reformed in the physical mixtures, which authorizes no negative relations between ATX and HPMC and DSLM.

3.3. Pre formulation studies

The angle of repose (25-30^{o}), Carr's index (<10%) and Hausner ratio (<1.1) indicates excellent flow properties of the granules and epitomized in the table 4.

Table 4. Flow parameters of prepared granules.

	Flow properties				
Formulation	**Angle of repose (^{0})**	**Bulk Density**	**Tapped Density**	**Carr's Index (%)**	**Hausner Ratio**
SRT-1	28.35±0.01	0.521±0.02	0.545±0.02	4.403±0.09	1.046±0.01
SRT-2	27.55±0.05	0.522±0.03	0.569±0.03	8.260±0.15	1.090±0.02
SRT-3	27.88±0.05	0.489±0.05	0.521±0.06	6.142±0.04	1.065±0.03
SRT-4	28.78±0.09	0.456±0.09	0.501±0.04	8.982±0.12	1.098±0.05
SRT-5	27.45±0.14	0.465±0.04	0.510±0.02	8.823±0.02	1.096±0.01
SRT-6	29.36±0.07	0.415±0.06	0.451±0.08	7.982±0.19	1.086±0.06

Readings in mean ±SD; The number of trials (n=3)

3.4. Post formulation studies

The prepared SRT were found to have a uniformity in thickness (5 mm) and weight which represents the drug and excipients were added and blended systematically. The loss on friability was negligible (1%) and the hardness was > 4 Kg/cm^2 indicates that the SRT having appreciable strength. The ATX content in SRT was found to be satisfactory as per the specifications (table 5). The *in vitro* discharge indicates controlled discharge of ATX from the formulation. Among the formulations SRT-5 showed controlled discharge for a prolonged period (Fig.2).

Table 5. Physical Characteristics of the prepared matrix table.

	Physical parameter				
Formulation	**Uniformity of weight (mg)**	**Hardness (cm^2)**	**Thickness (mm)**	**Friability (%)**	**Assay (%)**
SRT-1	250.8±1.05	4.9±0.02	4.55±0.02	0.58±0.02	97.9±2.05
SRT-2	250.4±2.42	5.8±0.06	4.51±0.05	0.28±0.01	95.9±2.17
SRT-3	251.1±1.98	4.7±0.04	4.55±0.06	0.29±0.01	96.7±1.26
SRT-4	252.7±2.04	5.6±0.08	4.52±0.02	0.47±0.03	96.6±2.33
SRT-5	250.5±1.25	6.1±0.09	4.51±0.09	0.33±0.02	98.4±2.84
SRT-6	250.8±0.96	5.7±0.01	4.53±0.01	0.39±0.02	96.9±2.27

Values in mean ±SD; The number of trials (n=3)

3.5. In vitro ATX release

The ATX release from the formulations was extended for more than 12h and shown in Fig.2.

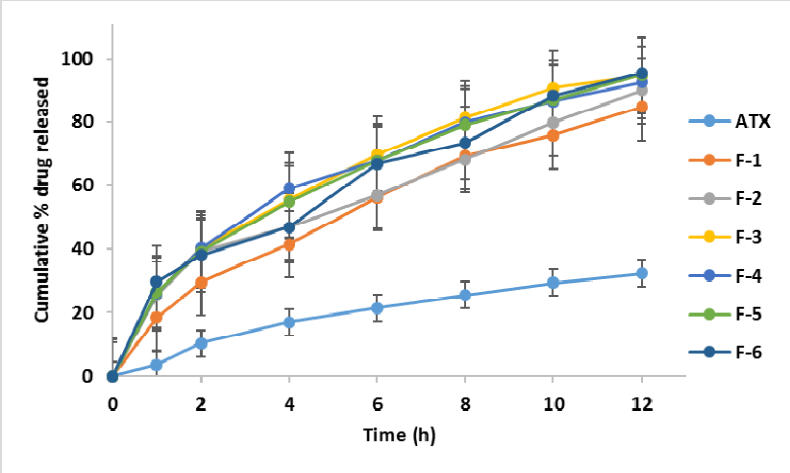

Fig. 2. Zero-order plots of prepared matrix tablets.

3.6. Discharge kinetics and mechanism

To know the mechanism of discharge and kinetics of ATX optimized formulation, SRT-5 was tried to fit into mathematical models and n, R^2 values for zero-order, first order (fig.3), Hixson Crowell's (fig.4) and Korsmeyer Peppas (fig.5) models were described in table 6. This study revealed that the ATX discharge from the devices followed non-fickian discharge for SRT-1, SRT-3, SRT-4, SRT-5 (as the 'n' value is >0.5) and Fickian for SRT-2 and SRT-6 (as the 'n' value is >0.5).

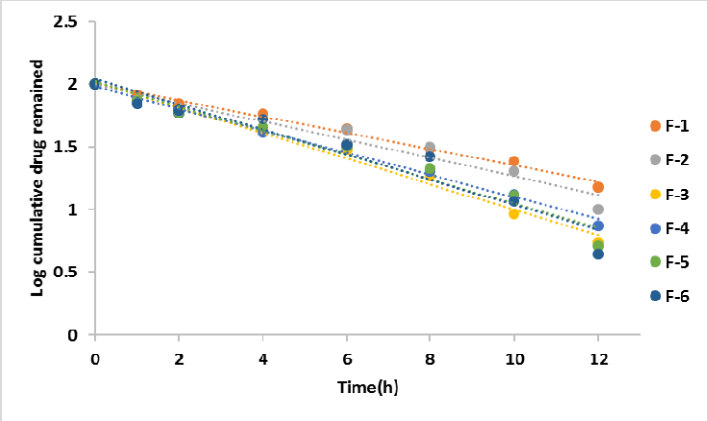

Fig. 3. First order plots of prepared matrix tablets.

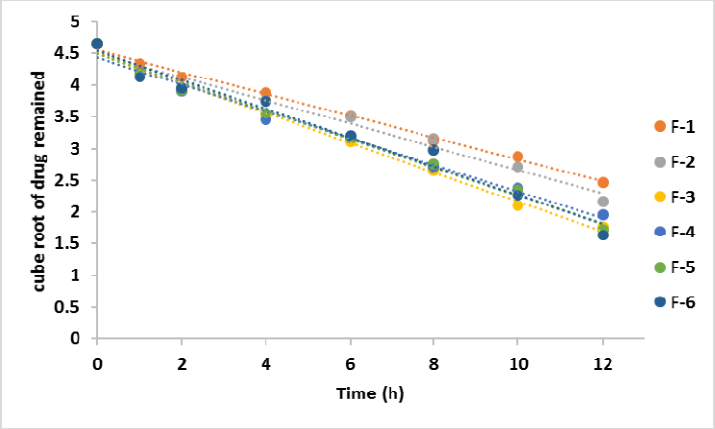

Fig. 4. Hixson Crowell's plots of prepared matrix tablets.

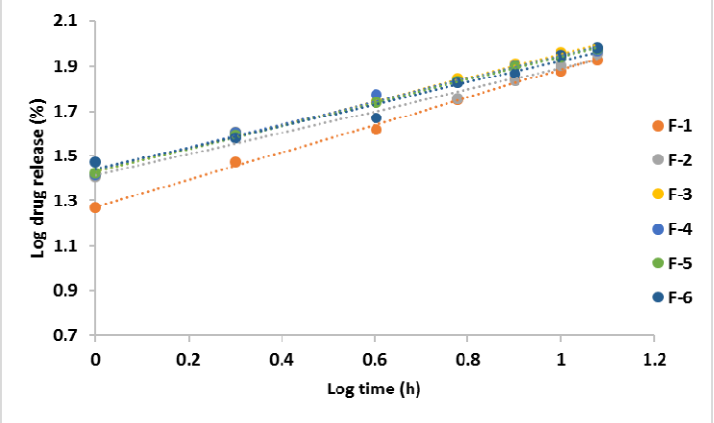

Fig. 5. Korsmeyer Peppas plots of prepared matrix tablets.

Table 6. Kinetic data of prepared matrix tablets.

Formulation	Model with correlation values				
	Zero-order	First order	Hixson Crowell's	Korsmeyer Peppas	
	R^2	R^2	R^2	R^2	n
SRT-1	0.9583	0.9905	0.9944	0.9970	0.6118
SRT-2	0.9314	0.9508	0.9728	0.9816	0.4777
SRT-3	0.9150	0.9859	0.9866	0.9961	0.5233
SRT-4	0.8979	0.9913	0.9905	0.9991	0.5113
SRT-5	0.9207	0.9668	0.9749	0.9918	0.5069
SRT-6	0.9357	0.9303	0.9933	0.9747	0.4814

4. CONCLUSION

The authors in this study observed that Atomoxetine matrix tablet extends the emission rate for prolonged duration more than 12 h with increased bioavailability and devoid of repetitive dosing and dose. This was also noted that *Datura stramonium* leaves mucilage can be a good polymer in

combination with HPMC for controlling the drug discharge with reduced adverse effects and cost and with improved the patient happiness and effectiveness.

5. ACKNOWLEDGMENTS

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6. ETHICAL ISSUE

Not Applicable.

7. CONFLICT OF INTEREST

None Declared.

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