Research Article

Available Online at: www.ijphr.com

International Journal of Pharmaceuticals and Health care Research

ISSN: - 2306 – 6091

FORMULATION AND EVALUATION OF FLUVOXAMINE MALEATE MATRIX TABLETS USING GUM KONDAGOGU

*Cherukuri Sowmya, Modala Santhosh Raja

Raghavendra Institute of Pharmaceutical Education and Research,

Anantapur, Andhra Pradesh, India - 515721.

Abstract

Gum Kondagogu is a naturally obtaining gum from the *Cochlospermum* species which is abundantly available in the forest regions of Andhra Pradesh. It has many pharmaceutical applications like matrix forming, film forming substance among them the controlled release nature had been explored. Fluvoxamine Maleate is a selective serotonin reuptake inhibitor and it has shown very good results when administered in controlled release dosage forms. The various matrix formulations have been prepared and evaluated for pre and post compression parameters which showed the results in acceptable limits. Among them the formulation containing 50% of Gum Kondagogu and 10% of HPMC K100M had shown a very similar release profile with that of commercial. The FTIR, DSC studies showed that there are no interactions between the excipients and the drug. The better formulation had shown a stable release profile after being kept for accelerated stability conditions for a period of three months. Kondagogu gum is a suitable rate controlling polymer for the preparation of once daily Fluvoxamine Maleate extended release tablets.

Keywords: Fluvoxamine maleate, Gum kondagogu, Matrix tablets.

Introduction

Oral administration of a drug has been the most convenient and commonly employed route of drug delivery as it offers the greater flexibility in the dosage form design[1, 2]. Designing of controlled release polymers offers some advantages such as release of the drug at a required delivery rate, constant blood levels of drug, reduction of dosing frequency and improved patient compliance[3,4]. However the development of oral controlled release formulations for water soluble drugs to achieve a constant release has always been a great release which includes bio adhesive systems[5], mirocapsules, swelling and expanding systems[6,7], but the matrix system is the most commonly adopted one for the preparation on oral controlled release dosage forms[8].

Fluvoxamine Maleate is categorized as selective serotonin reuptake inhibitor and is generally used in obsessive compulsory disorder[9,10]. It has an oral bioavailability of 50% and reaches its T_{max} in 2 to 8 hrs after single dose administration[11]. The effectiveness of Luvox CR capsules for the treatment of OCD was demonstrated in a 12 week, multicenter, placebo controlled study of adult outpatients. Patients in this trial were titrated in

Author for Correspondence:

C. Sowmya,

Dept. of Pharmaceutics,

Raghavendra Institute of Pharmaceutical Education and Research,

Saigram, KR Pally cross, Chiyyedu, Anantapur, Andhra Pradesh, India – 515721.

Email ID: drsowmyariper@rediffmail.com

50 mg increments over the first six weeks of the study on the basis of response and tolerance from a dose of 100 mg/day to a Fluvoxamine dose within a range of 100 mg to 300 mg once a day. Patients in this study had moderate to severe OCD, with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total scores of 26.6 and 26.3 for Fluvoxamine and placebo treatment groups, respectively. Patients receiving Luvox CR capsules demonstrated statistically significant improvement over placebo patients at the primary endpoint (week 12) compared to the baseline on the Y-BOCS. The mean daily dose of Luvox CR capsules administered to patients was 261 mg at end of study[12]. The aim of the proposed work is to study the rate controlling property of Gum Kondagogu. Gum Kondagogu is a naturally occurring gum from the forest regions of Andhra Pradesh. The pharmaceutical properties of the gum are very less explored. The present plan of work includes the preparation of matrix tablets by using gum Kondagogu and its drug release optimization with HPMC. The developed dosage forms were evaluated for various pre compression, post compression parameters and *in-vitro* dissolution studies. The selected formulations were subjected to stability testing. The interaction studies of the developed formulation were evaluated using Differential Scanning Calorimetry (DSC), FT-IR and UV Spectroscopy.

Materials and methods

Fluvoxamine Maleate, HPMC K100M were obtained as a gift sample from RA ChemPharma Ltd (Hyderabad). Gum Kondagogu was procured from Nutriroma Chemicals Pvt Ltd (Hyderabad, Pharma Grade B No:0505022012). Iso Propyl Alcohol was procured from SD Fine Chemicals (Mumbai). Lactose Mono hydrate, Magnesium stearate were procured from Hi Media Pvt Ltd (Mumbai). All other reagents used were of analytical grade.

Preparation of Tablets

The granules are prepared by wet granulation process[13]. All the ingredients are weighed accurately on electronic balance. Then the drug and the polymer are mixed according to geometrical dilution method and are triturated to remove any coarse particles. After trituration the lactose is added, mixed properly and triturated. IPA: water (1:1) solution is used as binding agent. The binder agent is slowly added with trituration to form dough. Then the dough is passed through sieve no 10 to produce granules. The formed granules are dried for about 10 to 15 min in a hot air oven. After drying granules are once again passed through sieve no 20.The Magnesium Stearate is passed through sieve no 200 and is mixed properly and evenly. The granules are weighed and punched with a hardness of 4 to 5 kg/cm^2 using 10 mm round flat faced punches on 12 station tabletting machine (Rimek Mini Press II). Tablet of each batch (batch size 40 tab) contained 65 mg of Fluvoxamine Maleate.The formulations of tablets with their codes were given in Table 1.

Table No. 01: Formulation table

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Fluvoxamine Maleate	65	65	65	65	65	65	65	65
Gum Kondagogu	90	120	150	180	210	150	150	150
HPMC K100M	-	-	-	-	-	30	45	60
Lactose	141	111	81	51	21	51	36	21
Magnesium Stearate	4	4	4	4	4	4	4	4

Evaluation of Granules[14, 15, 16]

Angle of repose the angle of repose was determined by funnel method was calculated by using the following equation:

$$\text{Tan } \theta = h/r$$

Where,

h = height of the powder pile

r = radius of the powder pile

Bulk density both Loose Bulk density (LBD), Tapped Bulk Density (TBD) were determined. These are calculated by using following formulas,

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility index was determined by using following formula,

Carr's index (%) = [(TBD- LBD) x 100]/TBD

Total porosity was determined by using the following formula

Porosity (%) = $[(V_{bulk} - V) \times 100]/V_{bulk}$

Drug content Powder equivalent to 100mg of Fluvoxamine Maleate was weighed and extracted in 6.8 pH phosphate buffer for 5hrs was filtered through 0.45µm membrane filter. The absorbance was measured at 246 nm after suitable dilution using 6.8 pH phosphate buffer as a blank and all experiments were conducted in triplicate. The results are shown in table 2,2.1

Table No. 02: Evaluation of granules

Formulation	Angle of repose ± SD*	LBD ± SD* g/ml	TBD ± SD* g/ml	Compressibility index (%) ± SD*	Hausner ratio ± SD*
F1	21.54 ± 0.016	0.458 ± 0.0023	0.556 ± 0.086	13.21 ± 0.086	1.12 ± 0.043
F2	22.68 ± 0.036	0.459 ± 0.0036	0.552 ± 0.064	14.23 ± 0.057	1.14 ± 0.037
F3	24.82 ± 0.071	0.462 ± 0.0029	0.576 ± 0.083	14.32 ± 0.069	1.16 ± 0.032
F4	20.89 ± 0.082	0.431 ± 0.0036	0.583 ± 0.075	14.68 ± 0.013	1.12 ± 0.016
F5	26.91 ± 0.092	0.462 ± 0.0052	0.531 ± 0.063	14.62 ± 0.008	1.18 ± 0.039
F6	25.42 ± 0.018	0.456 ± 0.0038	0.564 ± 0.018	13.29 ± 0.018	1.13 ± 0.032
F7	24.42 ± 0.014	0.434 ± 0.0056	0.546 ± 0.019	13.25 ± 0.009	1.14 ± 0.056
F8	23.68 ± 0.018	0.457 ± 0.0041	0.549 ± 0.018	13.45 ± 0.014	1.13 ± 0.034

***** represents mean ± SD* (n = 3)

Table No. 02.1: Evaluation of granules

Formulation	Percentage porosity ± SD*	Drug content(%) ± SD*
F1	34.62 ± 0.13	98.23 ± 0.018
F2	32.48 ± 0.26	99.62 ± 0.022
F3	28.26 ± 0.60	95.83 ± 0.068
F4	31.32 ± 0.82	95.66 ± 0.042
F5	26.21 ± 0.96	98.26 ± 0.098
F6	25.62 ± 0.82	98.39 ± 0.056
F7	29.35 ± 0.75	98.49 ± 0.089
F8	29.48 ± 0.48	99.42 ± 0.075

***** represents mean ± SD* (n = 3)

Evaluation of tablets[14, 15]

Thickness of the tablets was determined using vernier calipers(NSP suppliers, guntur) five tablets from each batch were used and average values were calculated.

Weight variation 20 tablets of each formulation were weighed using (LC GC) and the test was performed according to the official method

Hardness and friability the hardness and friability of each formulation was determined by taking 6 tablets from each using Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Electrolab EF2, Bombay, India) respectively.

Swelling index the swelling behavior of tablets was determined by the following method[17]

$SI = \{(M_t - M_o)/M_o\} X\ 100$

Where,

M_t = weight of tablet at time t

M_o = initial weight of the tablet

Determination of viscosity viscosity of the aqueous polymeric solution (2%wt/vol) was determined using Brookfield Viscometer (Amkette LV DV II Pro)

Drug content Six tablets were weighed individually from each batch and then powder them separately. Powder equivalent to 100 mg of drug was weighed and drug was extracted in buffer for 5 hrs. The resultant solution was filtered through 0.45µ membrane filter. The absorbance was measured at 246 nm after suitable dilution against blank. Results were shown in table no 3, 3.1.

Table No. 03: Evaluation of tablets

Formulation	Hardness Kg/cm^2 ± SD*	Thickness mm ± SD*	Friability % ± SD**	Weight variation % ± SD**	Drug content% ± SD***
F1	6.05 ± 0.012	3.11 ± 0.108	0.42 ± 0.06	1.032 ± 0.005	99.18 ± 0.057
F2	6.38 ± 0.021	3.62 ± 0.126	0.36 ± 0.02	1.040 ± 0.009	99.61 ± 0.028
F3	7.11 ± 0.018	3.22 ± 0.132	0.29 ± 0.04	1.028 ± 0.003	99.82 ± 0.036
F4	7.31 ± 0.028	3.18 ± 0.096	0.63 ± 0.09	1.030 ± 0.008	99.21 ± 0.041
F5	8.12 ± 0.053	3.53 ± 0.162	0.75 ± 0.03	1.084 ± 0.008	99.68 ± 0.052
F6	7.19 ± 0.048	3.17 ± 0.057	0.82 ± 0.12	1.039 ± 0.006	99.89 ± 0.082
F7	7.21 ± 0.045	3.21 ± 0.041	0.26 ± 0.16	1.027 ± 0.004	99.56 ± 0.048
F8	7.29 ± 0.036	3.41 ± 0.075	0.49 ± 0.29	1.028 ± 0.009	99.54 ± 0.072

Table No. 03.1: Evaluation of tablets

Formulation	Swelling index (%) ± SD*	Viscosity (cps) ± SD*
F1	117.25 ± 2.3	780 ± 15
F2	146.27 ± 1.6	960 ± 20
F3	156.25 ± 1.5	1147 ± 15
F4	201.25 ± 2.6	1418 ± 20
F5	238.24 ± 1.6	1500 ± 15
F6	160.25 ± 2.6	1210 ± 18
F7	170.48 ± 2.5	1310 ± 20
F8	180.24 ± 2.4	1390 ± 25

* represents average value ± SD (n = 6)
** represents average value ± SD (n = 20)
*** represents average value ± SD (n = 10)

***Invitro* dissolution studies**

Drug release from the Controlled Release tablets was studied using 8 station dissolution rate test apparatus (Electrolab) employing a paddle stirrer at 50 rpm and at 37 ± 1^{0}c. The dissolution medium consisted phosphate buffer of pH 6.8 (900ml). The drug release at different time intervals was measured by UV visible spectrophotometer (Systronics 2202) at 222nm developed method was validated and it was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The drug release experiments were conducted in triplicate. The dissolution experiment was also performed for commercial tablets. The release profiles were shown in fig:1 & 2.

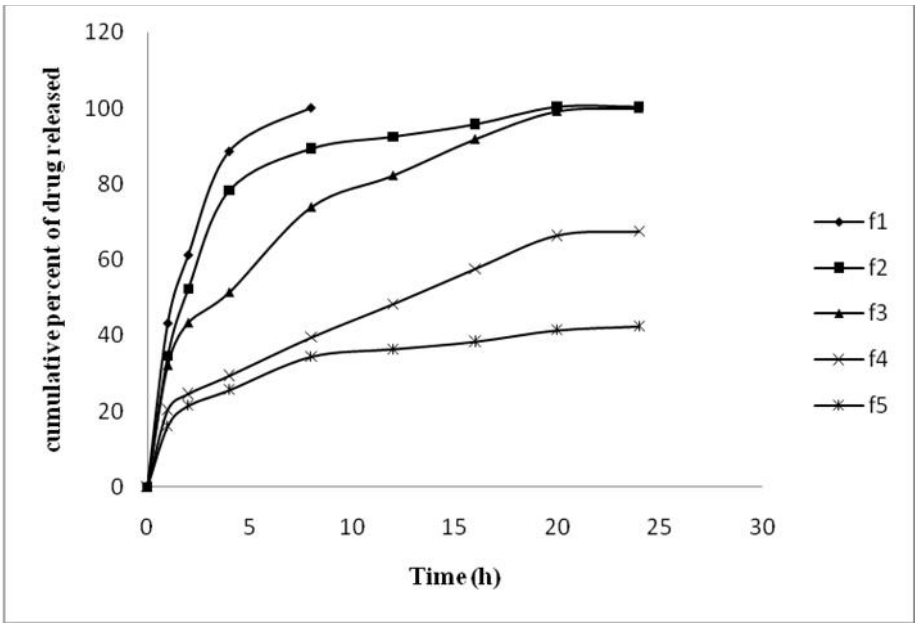

Fig. No. 01: Release profiles of different formulations of Fluvoxamine with gum Kondagogu

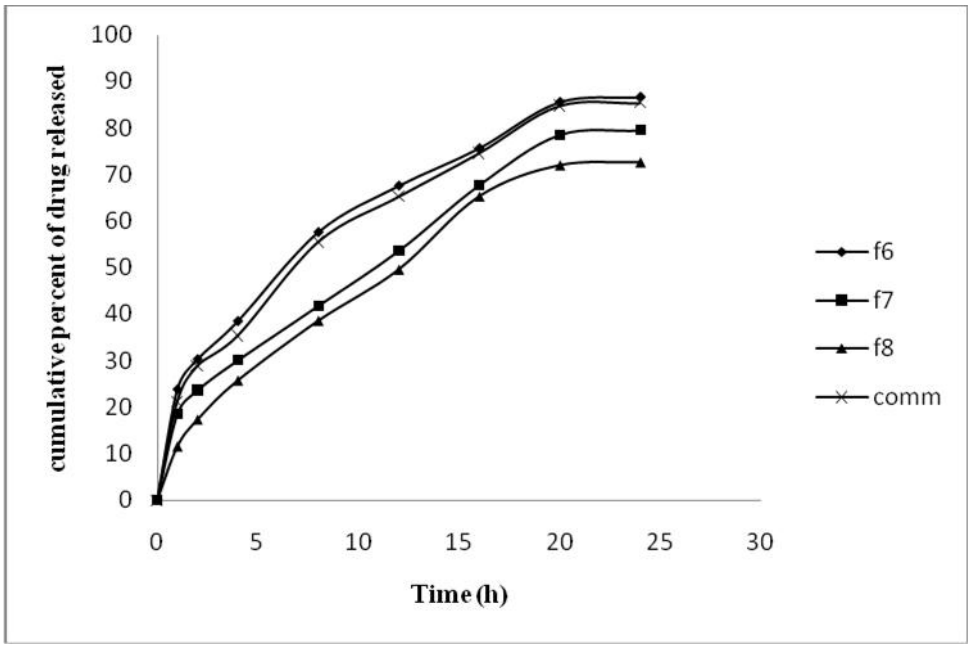

Fig. No. 02: Release profiles of different formulations of Fluvoxamine Maleate in combination with Gum Kondagogu, HPMC and Commercial

Study of release kinetics: The dissolution data was fitted into the following mathematical models**.** Zero order equation $Q = Q_0 - k_0t$, First order equation $\ln Q = \ln Q_0 - kt$, Higuchi equation[18] $Q = k_2t^{1/2,}$ Korsemeyer and Peppas equation[19] $Q/Q_0 = kt^{n.}$ Where k_0, k_1, k_2 were release rate constants, Q/Q_0 was fraction of drug released at time t, k was a constant, n is the release exponent indicates mechanism of release. If n< 0.5, fickian diffusion mediated release occurred, if n value is between 0.5 to 1.0 anamolous release (i.e diffusion coupled with polymer matrix relaxation) occurred and erosion (i.e complete matrix relaxation) mediated release occurred in n = 1 for supercase transport II n value is > 1. Correlation coefficient values and Release kinetics of matrix tablets were shown in Table 4 & 5.

Table No. 04: Correlation coefficient (r) values in the analysis of release data of Fluvoxamine matrix tablets as per various kinetic models

Formulation code	Correlation coeffecient (r^2)			
	Zero order	First order	Higuchi	Peppas
F3	0.8245	0.9717	0.9818	0.9932
F4	0.9009	0.9727	0.9874	0.9617
F5	0.7201	0.7851	0.9370	0.9862
F6	0.8845	0.9925	0.9954	0.9899
F7	0.9496	0.9869	0.9836	0.9690
F8	0.9665	0.9964	0.9848	0.9982

Table No. 05: Release characteristics of different formulations of Fluvoxamine matrix tablets

Formulation	T_{50} (h)	T_{90} (h)	$K_1(h^{-1})$	'n' in Peppas equation
F3	4	15.6	0.1561	0.38
F4	13	>24	0.0497	0.38
F5	>24	>24	0.0227	0.32
F6	6.6	>24	0.0923	0.43
F7	9.8	>20	0.0732	0.47
F8	12	>20	0.0617	0.60

Interaction studies: Differential scanning calorimeter (DSC) and FT-IR and UV spectral studies were performed to characterize formulation for excipient compatibility. FT –IR spectra were recorded by using KBr disc as references on FT IR spectrophotometer (Bruker). The FT IR spectra were shown in fig 3 to 5. DSC studies were carried out using Metler TA 4000 system DSC 25 and thermograms were recorded for pure drug and formulation were shown in fig: 6 to 9.

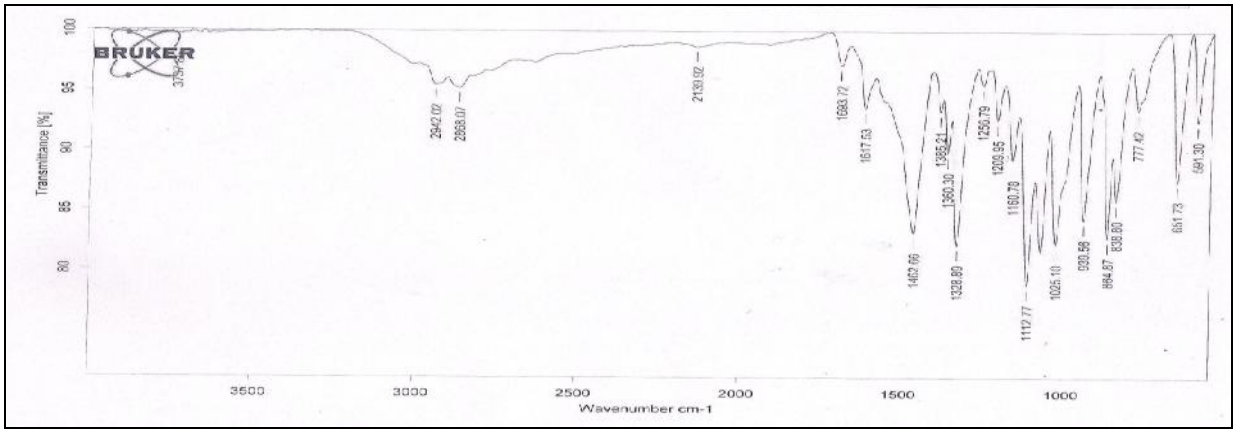

Fig. No. 03: FT-IR spectrum of pure Fluvoxamine Maleate

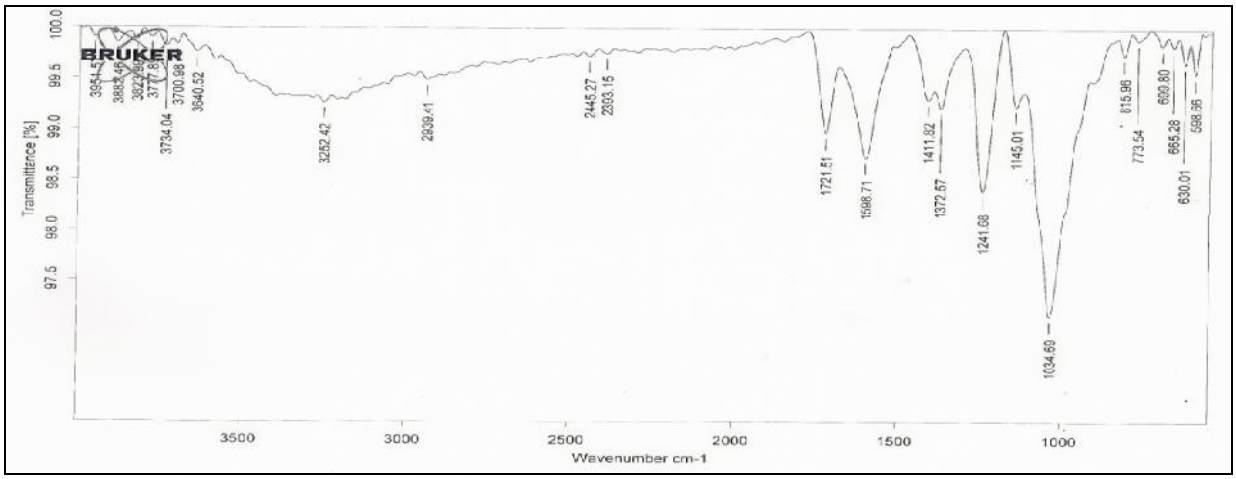

Fig. No. 04: FT-IR spectrum of Gum Kondagogu

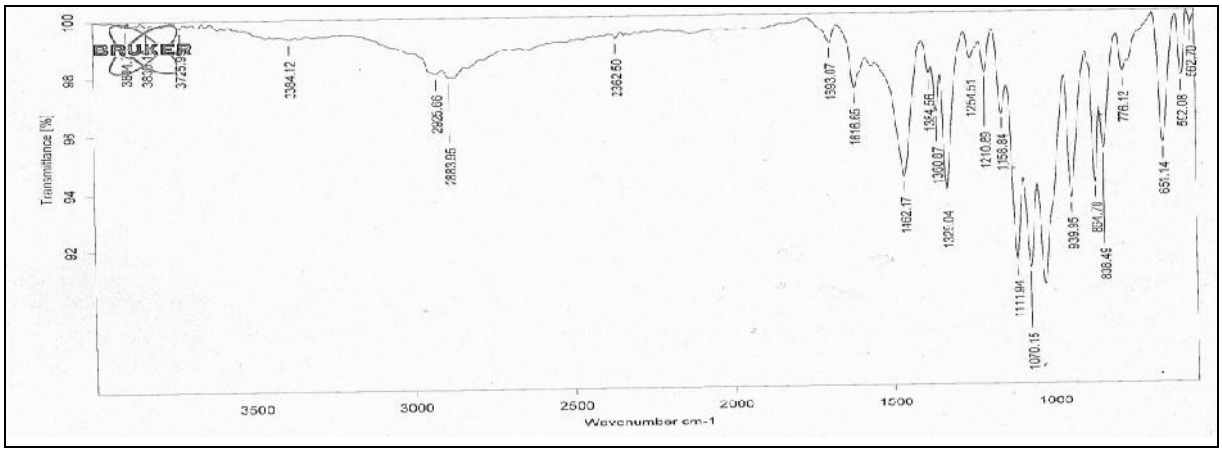

Fig. No. 05: FT-IR spectrum of final formulation

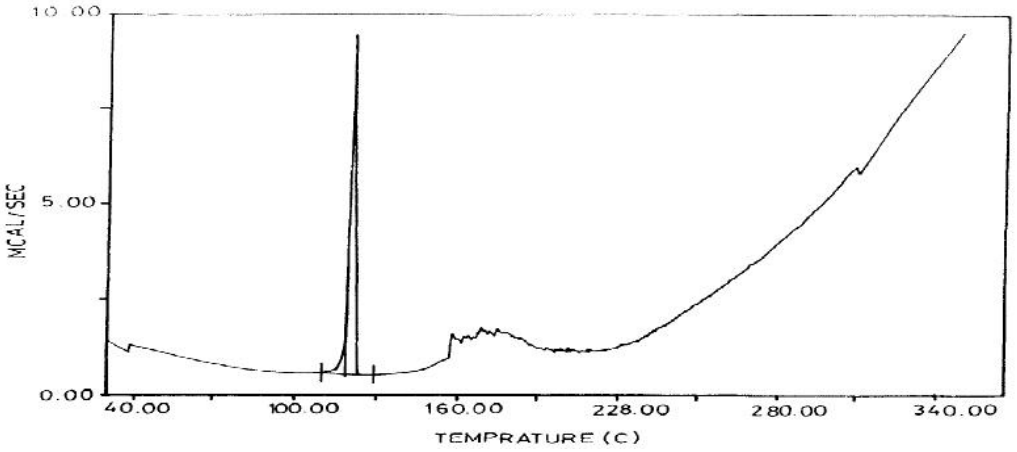

Fig. No. 06: DSC thermogram of Fluvoxamine Maleate

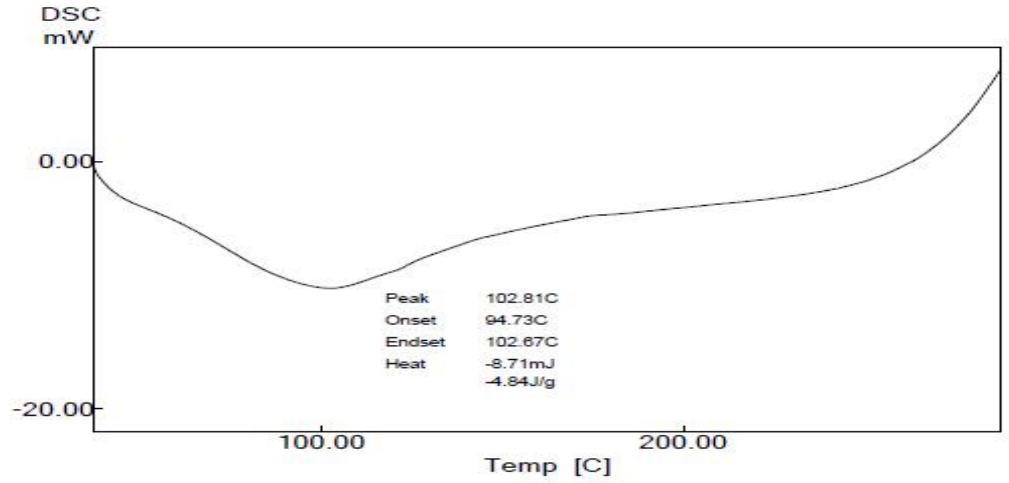

Fig. No. 07: DSC Thermogram of gum Kondagogu

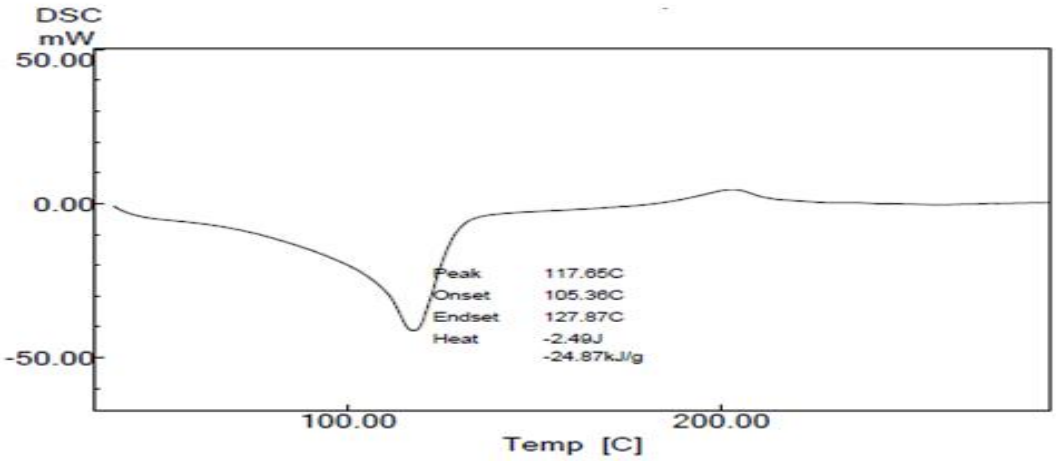

Fig. No. 08: DSC thermogram of final formulation

Stability studies[20]: The stability studies were performed as per ICH guidelines at conditions of temperature and 40^0c and 75% RH using stability chambers for three months. The samples were analyzed for drug content.Release profile of drug before and after storage for three months were shown in Fig;9.

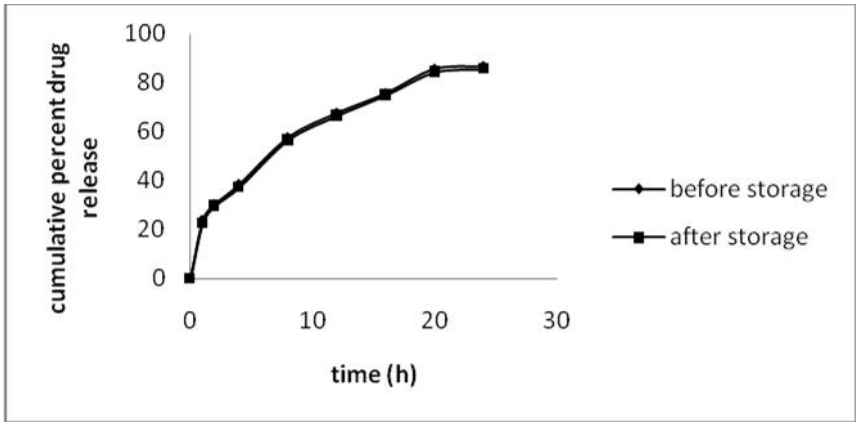

Fig. No. 09: Release profile of F6 before and after storage for 3 months

Results and discussion

The granules prepared were evaluated for Angle of Repose, LBD, TBD, Compressibility Index, Hausner ratio, Percentage Porosity and drug content, results were shown in tableno:2,2.1. The results of Angle of Repose, Compressibility Index and Hausner ratio ranged from 20.89 ± 0.082 to 26.91 ± 0.092, 13.21 ± 0.086 to 14.68 ± 0.013 and 1.12 ± 0.0016 to 1.18 ± 0.039 respectively. The results of LBD and TBD ranged from 0.431 ± 0.0036 to 0.462 ± 0.0052 and 0.531 ± 0.0063 to 0.583 ± 0.0075 respectively. The results of percentage porosity ranged from 25.62 ± 0.82 to 34.62 ± 0.13. The drug content in a weighed quantity granules of prepared formulations ranged from 95.66 ± 0.042 to 99.62 ± 0.022%. Matrix tablets each containing 65mg of Fluvoxamine could be prepared by conventional wet granulation method. All the formulations showed uniform thickness ranging from 3.11 ± 0.108 to 3.62 ± 0.126 mm. Hardness of the tablets was in the range of 6.05 – 8.12 kg/cm^2. Loss in the friability test was less than 0.82% in all the cases. The results of the swelling index ranged from 117.25 – 238.24. All the tablets were found to be non-disintegrating in water, acidic (pH1.2) and alkaline (pH 6.8) fluids. The results were shown in table 3, 3.1.

The formulations coded with F1, F2, F3, F4, and F5 composed of 30%, 40%, 50%, 60% and 70% of Gum Kondagogu. The results of dissolution studies of these tablets showed the release of 43.24%, 34.51%, 32.21%, 20.32% and 16.06% of Fluvoxamine at the end of 1 hrs. The formulations coded with F6, F7, F8 composed of 50% of gum and 10%, 15% and 20% of HPMC. These tablets showed the release of 23.76%, 18.42% and 11.52% of Fluvoxamine Maleate at the end of 1hrs and 85.52%, 78.43%, 71.96% at the end of 20 hrs.

The formulations were further modified by incorporating different combinations of HPMC. The release of Fluvoxamine from all the matrix tablets formulated followed first order kinetics and the K_1 for F6 was found to be 0.0293 hr^{-1}, the formulations showed fair linearity, with r^2 values between 0.7851 and 0.9964. results were shown in table no:4.

The results of the angle of repose (<30) indicates good flow properties of the granules. This was further confirmed by lower compressibility index (<15%) values and lower Hausner ratio values. Loose bulk Density (LBD), Tapped Bulk Density (TBD) of the granules were <0.5 and <0.6 g/ml respectively and are more uniform values indicates that the prepared granules were of in uniform size. Percentage porosity values below 26% shoes the particles in the powder of greatly different sizes and if values were greater than 48% shows that the particles in the powder are in the form of aggregates or flocculates**.** The developed granules possessed satisfactory flow properties, compressibility index, Hausner ratio and drug content. Hardness of the tablets indicates that as the concentration of gum increases the hardness also increases. The average percentage deviation of all the prepared tablets was found to be within the pharmacopoeia limits. The formulation containing 50% of Gum Kondagogu (F3) showed release of 100.2% at the end of 20hrs but the other two formulations failed to meet the specifications of USP for controlled release so the F3 was selected for further study.

The results of the dissolution studies of F1, F2, F3, F4 and F5 formulations indicated that the drug release was decreased with increasing in the concentration of the gum, (Fig:1). This is due to the increased swelling and viscosity of the dispersion with the usage of increased concentration of Gum Kondagogu. In case of F6, F7, and F8 the amount of drug released was reduced with increasing concentration of HPMC,(Fig:2). This may be due to increased viscosity of the dispersion and formation of gel state with dissolution medium. The formulations made with gum alone like F1, F2, F3 had released nearly 100 percent of drug within 8, 20, 20hrs, formulations made with Gum Kondagogu and HPMC were taken 24 hrs to release 100% of drug. The formulations prepared by using the combinations of Gum Kondagogu and HPMC released 90% of the drug in 24 hr for F6. Gum Kondagogu forms a swelling gel by the addition of HPMC as it forms porous swellable matrix desired release profile was achieved. The results of the stability studies indicated that there is no significant change in the drug content and release profiles.(Fig:9). To confirm the diffusion mechanism the data was fitted into Korsemeyer et al equation, developed formulations showed good linearity (r^2 = 0.9617 to 0.9982) with release exponent (n) value ranging from 0.32 to 0.60, indicating that diffusion is the predominant mechanism of drug release from all the developed formulations. When fitting the data in Higuchi and Korsemeyer et al equation the F6 formulation showed high linearity r^2 of 0.9954 and r^2 = 0.9899 respectively with slope (n) value of 0.43 (Table no:4 &5). This n value of formulation indicates the release of drug that is fickian diffusion from F6 formulation.The formulation comprising of 50% of gum Kondagogu, 10% of HPMC K 100 M was able to control the release of Fluvoxamine Maleate for 24 hrs and also showing comparable release profile with that of commercial. The 50% of gum Kondagogu was the suitable concentration to prepare sustained release matrix tablets. Hence gum Kondagogu is a suitable rate controlling polymer for the preparation of once daily Fluvoxamine Maleate extended release tablets.

Acknowledgement

The authors are thankful to Dr.K.MadhavaChetty, Assistant Professor, Department of Botany, Sri Venkateswara University, Tirupathi, A.P, India for authenticating the procured Gum Kondagogu.

References

1. Robbinson JR, Vincent HL Lee, Fundamentals of Controlled drug delivery. In:Controlled drug delivery fundamentals and applications, 2nd ed.Informa Health Care, New York,.vol 29; 2009,1-23.
2. Haan PD, Lerk CF. Oral controlled release dosage forms a review. Pharma world and science, 6(2) 1984,57-67.
3. Kale SN, Gudsoorkar VR, Shete JL. Solid dispersions of Piroxicam using PEG 6000. Eastern pharmacist; 36(423), 1993,125-127.
4. Brabander C, Veravet C, Remon JP. Development and evaluation of sustained release mini matrices prepared via hot melt extrusion. J. of Control.Rel., 89(2) 2003, 235-247.
5. Santus G, Lazzarini C, Bottoni G, Sandefer EP, Page RC, Doll WJ, Ryo VY, Digenis GE. An invitro- in vivo investigation of oral bioadhesive controlled release furosemide formulations. E. J. of Pharmaceutics and Biopharm., 44(1), 1997, 39-52.
6. Deshpande AA, Rhodes CT, Shah NH, Mallick AW. Controlled release drug delivery systems for prolonged gastric residence. Drug development and industrial pharmacy., 22(6) 1996, 531-539.
7. Deshpande AA, Rhodes CT, Shah NH, Mallick AW. Development of a novel controlled release system for gastric retention. Pharmaceutical research, 14(6) 1997, 815-819.
8. Raghuram Reddy K, Srinivas M, Srinivas Reddy. Once daily sustained release matrix tablets of nicorandil formulation and invitro evaluation. AAPS Pharm Sci tech, 4(4) 2003,no 61.
9. *United States pharmacopoeia*, USP 29-NF24. The United States Pharmacopoeial Convention, Rockville.964.
10. Foda NH, Radwan MA, Aldeeb OA.Analytical profiles of drug substances and excipients. Editor Brittain HG. Vol 24: 165-208.
11. Irons J., Fluvoxamine Maleate in treatment of anxiety disorders. Neuropsy disease and treatment. 1(4), 2005, 289-299.

12. Luvox CR prescribing information, Abott laboratories, distributed by Jazz pharma.
13. Banker GS, Anderson LR. Tablets. In: The Theory and Practice of Industrial Pharmacy,special Indianed, Leon Lachman, Herbert A Lieberman. CBS Publishers and Distributors Pvt Ltd, Delhi., 1987,293-345.
14. Cooper J, Gunn C. Tutorial pharmacy, Sixth ed,Carter SJ. CBS Publishers and Distributors, New Delhi,1986, 211-233.
15. James Wells. Pharmaceutical preformulation: the physicochemical properties of drug substances. In: Pharmaceutics: The science of dosage form design, Second ed, Aulton M.E. Churchill Livingstone, Edinburgh, 1986, 134.
16. Patrick J Sinko. Martin's Physical Pharmacy and Pharmaceutical sciences, Sixth ed, Lippincott Williams and Wilkins, Philadelphia, 2011, 465-466.
17. Jain N.K. Introduction to Novel drug delivery systems, VallabhPrakashan, New Delhi, 2010,116.
18. Higuchi T. Mechanism of sustained action medication- theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J of pharmaceutical sciences 52(12) 1963, 1145.
19. Ritger PL, Peppas NA. A simple equation for description of solute release Fickian and non fickian release from non swellable devices in the form of slabs, spheres, cylinders or discs. J of Controlled Release 5(1), 1987, 23-36.
20. ICH guide lines on stability testing Q1C, November 1996.