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Original Article

FORMULATION AND EVALUATION OF FLUVOXAMINE CONTROLLED RELEASE TABLETS

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ABSTRACT

A controlled drug delivery system is usually designed to deliver the drug at the particular rate. The performance of a drug presented as a controlled-release system depends upon its release from the formulation. Movement within the body during its passage to the site of action. The former depends upon the fabrication of the formulation and the physicochemical properties of the drug while the latter element is dependent upon pharmacokinetics of drug. In comparison to conventional dosage form where the rate-limiting step in drug availability is usually absorption through the biomembrane, the rate-determining step in the availability of a drug from controlled delivery system is the rate of release of drug from the dosage form which is much smaller than the intrinsic absorption rate for the drug. The objective of the development programme was to formulate a robust, stable formulation of Fluvoxamine controlled release tablets 100mg comparable to the reference product Fluvoxin CR 100mg(Luvox) in terms of in-vitro dissolution profile. Matrix tablets were compressed without any problem and do not require any change in ratio of excipients in formulation. Results of the present study demonstrated that hydrophilic polymers could be successfully employed for formulating controlled-release matrix tablet of fluvoxamine. Formulations containing polymer percentage 15% controlled the drug release for 12 h. The combination of drug Fluvoxamine, lubricant [SSF] and glidant[Aerosil] was showed high drug release profile. Wet granulation method was found to be better choice to extend the drug release for 12 h. Film coating of tablet is beneficial for protecting the drug.

Keywords: Controlled release tablet, Orally controlled drugs, Rate determining step, Controlled drug delivery systems, Fluvoxamine.

INTRODUCTION

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug [1-5]. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug's pharmacokinetics [5].

More precisely, controlled delivery can be defined as Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects [6,7]. Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue [8].

Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type. Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body [9-14].

Advantages of controlled drug delivery system

1. Overcome patient compliance problems.

2. Employ less total drug: Minimize or eliminate local side effects, Minimize or eliminate systemic side effects, Obtain less potentiating or reduction in drug activity with chronic use, Minimize drug accumulation with chronic dosing.

3. Improve efficiency in treatment: Cures or controls condition more promptly, improves control of condition i. e., reduced fluctuation in drug level, Improves bioavailability of some drugs, Make use of special effects, e. g. Sustained-release aspirin for morning, Relief of arthritis by dosing before bed time.

4. Reduction in health care costs through –Improved therapy, Shorter treatment period, Lower frequency of dosing, and Reduction in personnel time to dispense, administer and monitor patients [15].

Disadvantages of controlled drug delivery system

1. Decreased systemic availability in comparison to immediate-release conventional dosage forms. This may be due to – Incomplete release, Increased first-pass metabolism, Increased instability, Insufficient residence time for complete release, Site-specific absorption, PH-dependent solubility.

2. Poor *in vitro – in vivo* correlation.

3. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

4. Reduced potential for dose adjustment of drugs normally administered in varying strengths.[16]

Oral controlled drug delivery systems

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action [17].

MATERIALS AND METHODS

Materials

Fluvoxamine maleate is a gifted sample from RA chem pharma, Maize starch, HPMCK4M and HPMC K15MM are procured from Colorcon-asia,munbai, HPMC K100M is obtained from Feichang-rutoi pharma, Sodium steril fumarate is obtained from JRS pharma,hyd, Aerosil is procured from Evonik degussa, HPMC606 is obtained from ShinEtsu, PEG 6000 is obtained from Clarient chemicals Ltd, FDC blue no-1 is obtained from Roha dye chem, Titanium dioxide is obtained from Kronos-germany.

Preparation of fluvoxamine maleate tablets

All the matrix tablets, each containing 100 mg of Fluvoxamine maleate, were prepared by wet granulation method and some of the formulations were prepared by using HPMC 100M, HPMCK15M & HPMC K4M to study the effect of Polymer on the drug release.

Step.1, Sifting: Fluvoxamine maleate**,** diluent (Maize starch), HPMC, SSF, colloidal silicon dioxide were sifted through sieve No. 40 separately.

Step.2, Dry mixing: Fluvoxamine maleate**,** diluents (Maize starch), HPMC were mixed in Rapid mixer granulator at 100rpm for 5-7 minutes.

Step.3, Binder preparation: Purified water used as a solvent and binder solution.

Step.4, Wet mixing: The dry mixed contents of step.2 were mixed for 9 minutes by adding the binder solution at main impeller speed of 150 rpm. After complete addition of binder solution, switch off the impeller. Scrap the sides of the blades. The process was restarted with main impeller speed of 100 rpm continued mixing till consistent granules were obtained. (use additional purified water to get proper wet mass consistency, if required)

Step.5, Wet screening: Wet granules were passed through #8 and transfer to fluid bed dryer.

Step.6, Drying: The granules were dried in FBD equipment by maintaining inlet temp. at 45^0c±5^0c till loss on drying of the granules NMT 1.0% obtained.

Step.7, Sifting: Dried granules were sifted through sieve #22.

Step.8, Lubrication: Sodium stearyl fumerate and colloidal silicon dioxide were transferred into conta blender and mix for 2 min with 15 rpm.

Step.9, Compression: Fluvoxamine CR tablets 100 mg compressed using 09.0 mm round, biconcave punches at optimum machine speed.

Step.10, Coating solution preparation: Take purified water in a clean vessel and dissolve weighed quantity of PEG 6000 and HPMC 606 stirring to get uniform dispersion under continuous stirring. Then add titanium dioxide and FD&C Blue no.1 with stirring to get uniform dispersion.

Step.11, Coating: The above solution was used to coat the core tablets. Maintain the tablet bed temp. at 50^0c ±5^0c.

Formulations: As following

Table 1: Composition of matrix tablets containing HPMC k100m*

F. Code	API(mg)	Maize starch (mg)	HPMCK 100M (mg)	P. Water (mL)	SSF (mg)	Aerosol (mg)	Total (mg)
F1	100	141.596	25.2	Qs	2.8	2.044	271.64
F2	100	149.996	16.8	Qs	2.8	2.044	271.64
F3	100	158.396	8.4	Qs	2.8	2.044	271.64
F4	100	163.996	2.8	Qs	2.8	2.044	271.64

Table 2: Composition of matrix tablets containing HPMC K15M*

F. Code	API (mg)	Maize starch (mg)	HPMCK 15M (mg)	P. Water (mL)	SSF (mg)	Aerosol (mg)	Total (mg)
F5	100	133.196	33.6	Qs	2.8	2.044	271.64
F6	100	141.596	25.2	Qs	2.8	2.044	271.64
F7	100	149.996	16.8	Qs	2.8	2.044	271.64
F8	100	158.396	8.4	Qs	2.8	2.044	271.64
F9	100	163.996	2.8	Qs	2.8	2.044	271.64

Table 3: Composition of matrix tablets containing HPMC K4M

F. Code	API (mg)	Maize starch (mg)	HPMC K 4M (mg)	P. WATER (mL)	SSF (mg)	Aerosol (mg)	Total (mg)
F10	100	163.996	2.8	Qs	2.8	2.044	271.64
F11	100	158.396	8.4	Qs	2.8	2.044	271.64
F12	100	149.996	16.8	Qs	2.8	2.044	271.64
F13	100	141.596	25.2	Qs	2.8	2.044	271.64
F14	100	133.196	33.6	Qs	2.8	2.044	271.64
F15	100	124.796	42	Qs	2.8	2.044	271.64

Table 4: Drug and Excipients compatibility studies on 15th and 30th day

S. No.	Test on 15th day	Test Conditions			
		25°C/60% RH	30°C/65% RH	40°C/75% RH	60°C
1	Description	White coloured free flowing powder	Yellow coloured free flowing powder	Yellow coloured free flowing powder	Yellow coloured free flowing powder
2	Assay (%)	99.8	99.7	99.9	100.2
3	Moisture content (%)	1.62	1.54	1.48	1.36

S. No.	Test on 30th day	Test Conditions			
		25°C/60%RH	30°C/65%RH	40°C/75%RH	60°C
1	Description	Yellow coloured free flowing powder	Yellow coloured free flowing powder	Yellow coloured free flowing powder	Yellow coloured free flowing powder
2	Assay (%)	99.8	99.7	99.9	100.2
3	Moisture content (%)	1.62	1.53	1.48	1.35

Based on the above results as shown in table 4 indicated that, there was no interaction between the drug substances and the chosen excipients and hence these excipients were considered for the use in the development of the formulation.

RESULTS AND DISCUSSION

Preformulation studies

Fourier transform infrared spectroscopy (FTIR)

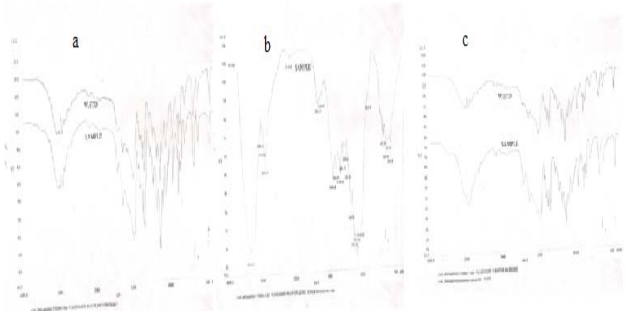

Fig. 1: a) API b) placebo c) optimized drug

The FTIR spectrum analysis as shown in fig. 1 showed that there is no appearance or disappearance of any characteristic peaks of pure Fluvoxamine maleate and in the physical mixture of drug with polymer and excipients. And the peak in placebo spectra confirms the excipient's peaks in the mixture. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and does not prone to any changes during formulation.

Physical evaluation of matrix tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in table 5 and 6. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 270 and 287 mg. The hardness of the tablets ranged from 70 to 90 N and the friability values were less than 1% indicating that the matrix tablets were compact and hard. The thickness the tablets ranged from 4.35 to 4.75 mm. All the formulations satisfied the content of the drug as they contained 90 to 101 % of Fluvoxamine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practice within control.

Table 5: Physical properties of precompression blend

COMP	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	32.5	0.56	0.61	8.20	1.089
F2	31.6	0.55	0.62	11.29	1.127
F3	28.4	0.575	0.635	9.45	1.104
F4	27.2	0.607	0.647	6.18	1.066
F5	35.34	0.569	0.630	9.68	1.107
F6	32.96	0.592	0.631	6.18	1.066
F7	32.06	0.55	0.62	11.29	1.127
F8	31.01	0.566	0.626	9.58	1.106
F9	29.98	0.611	0.639	4.38	1.046
F10	29.81	0.607	0.647	6.18	1.066
F11	30. 02	0.571	0.62	7.90	1.086
F12	27.64	0.601	0.641	6.24	1.067
F13	25.09	0.614	0.646	4.95	1.052
F14	27.74	0.556	0.612	9.15	1.10
F15	27.6	0.567	0.62	8.5	1.093

Table 6: Physical evaluation of matrix tablets

Formula Code	Hardness (N)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
F1	71.4±1.15	4.35±0.07	278.15±4.16	0.05	95.35±1.14
F2	73±4.09	4.34±0.07	276.2±5.17	0.06	94.28±0.80
F3	84±3.11	4.44±0.05	282.4±3.21	0.04	99.12±2.47
F4	90±1.0	4.47±0.04	271.3±6.24	0.08	99.53±1.87
F5	76±2.53	4.63±0.05	278±4.79	0.19	100.24±1.25
F6	81±3.06	4.54±0.07	277.9±5.23	0.13	98.57±1.22
F7	78±3.53	4.59±0.09	275±4.78	0.12	98.25±1.37
F8	85.1±3.22	4.49±0.03	274±6.11	0. 17	91.29±0.98
F9	86±1.00	4.51±0.05	279±4.21	0.14	96.34±2.18
F10	79±3.01	4.63±0.06	274±3.85	0.11	99.28±1.12
F11	82.3±2.21	4.48±0.09	276.4±5.26	0.08	97.35±0.43
F12	85.2±2.65	4.72±0.4	268.9±7.62	0.09	98.88±0.88
F13	88.6±3.22	4.62±0.07	272.6±4.69	0.05	101.22±0.88
F14	85.2±4.11	4.44±0.05	284.2±3.23	0.02	100.24±0.25
F15	83.1±3.14	4.35±0.03	282.5±5.35	0.01	101.6±1.20

Table 7: *In vitro* drug release data from HPMC K 100 M Matrices

Time (hours)	Innovator	F1	F2	F3	F4
0	0	0	0	0	0
1	14.4	2.2±0.8	3.6±2.3	5.01±0.2	5.2±2.4
2	23.4	4.3±0.4	5.2±3.1	6.3±1.2	6.9±0.1
4	36.3	7.3±1.4	7.9±2.9	8.6±2.3	9.8±0.1
6	50.3	9.4±1.8	10.2±1.4	11.8±0.8	13.1±1.2
8	62.7	10.8±1.1	12.9±1.2	14.3±2.1	14.6±3.4
12	90	12.3±1.9	15.2±1.5	17±2.6	19.1±2.3

***In-vitro* release data of fluvoxamine**

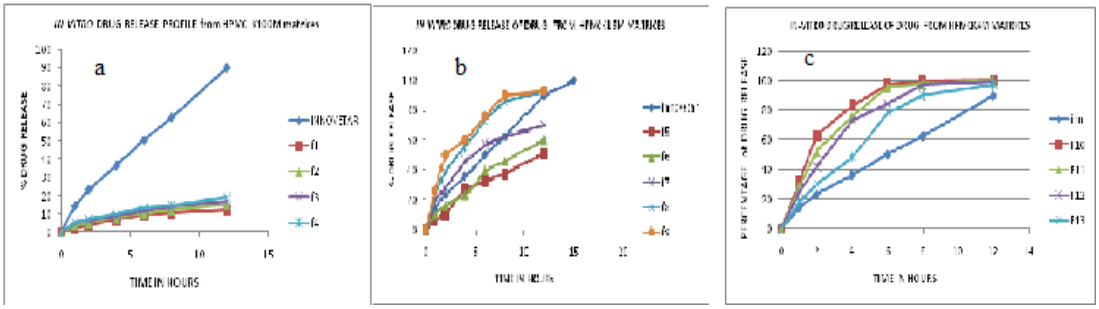

Fig. 2:a) *In-vitro* drug release profiles of fluvoxamine from HPMC K 100M Matrices b) *In-vitro* drug release profiles of fluvoxamine from HPMC K15M matrices *c) In-Vitro* drug release profiles of fluvoxamine from HPMC K4M matrices

Table 8: *In-vitro* drug release data of fluvoxamine from HPMC k15m matrices

Time(hr)	Innovator	F5	F6	F7	F8	F9
0	0	0	0	0	0	0
1	14.4	6.1±0.5	10.7±0.2	19.4±2.3	23.1±1.1	26.2±0.5
2	23.4	10.2±2.4	16.3±1.2	28.2±1.4	39.2±0.2	50.4±1.7
4	36.3	27.8±0.4	23.2±1.4	46.1±2.1	55.7±0.9	60.6±0.8
6	50.3	32.5±2.2	39.7±2.1	56.9±0.3	73.4±1.3	76.3±2.4
8	62.7	37.1±1.4	45.5±1.1	62.5±1.4	85.7±2.3	90.1±1.7
12	90	51.5±1.6	60.3±0.9	70.1±2.2	97.7±0.7	99.4±0.2

Table 9: *In-vitro* release data of fluvoxamine from hpmc k4m matrices

Time (hours)	Innovator	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0	0
1	14.4	32.1±0.2	28.4±1.3	25.2±0.1	17.8±2.4	17.3±0.4	15.3±1.4
2	23.4	63.1±0.1	52.1±1.7	41.7±1.1	29.9±0.3	25.5±2.3	23.5±1.1
4	36.3	83.4±1.6	75.4±2.0	73.4±1.5	48.6±0.6	38.6±1.1	36,6±0.7
6	50.3	97.4±0.3	95.2±1.5	84.2±2.3	78.3±1.5	45.8±0.5	47.9±2.1
8	62.7	99.8±1.2	97.4±1.1	97.6±2.9	90.1±1.3	69.8±0.5	63.2±1.5
12	90	100.4±2.7	99.8±2.5	99.4±1.5	97.4±2.0	95.8±1.4	91.2±1.6

The results of release studies of formulations F1 to F4 are shown in table 7 and fig. 2. Here the matrix tablets were formulated using HPMCK100M which is very viscous in nature. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer decreased, the kinetics of release increased.

Formulation F1 composed of 9% polymer, failed to release the minimum amount of drug. It releases only 1/4 of the drug in 12 hours. So percentage is decreased up to 6.1% in F2, 3.0% in F3 and finally 1% in F4. As the percentage of polymer decreased, the kinetics of release increased. This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core. But slow erosion is take place, so it's (F4) failed to release half amount of drug in 12 hours even with minimum amount of polymer i. e 1%.

In this formulation HPMC K15M was taken as release retarding agent, which is less viscous than HPMCk100M. drug release is as shown in table 8 and fig. 2. At first when 12% of polymer is used, only 50% of drug was released. So it is decreased to 9.2% in F6 and 6.18% in F7, even though they failed to release the required amount of drug. Further decreases in polymer concentration shows too much releases in first 6 hours. Here erosion of tablet is very high. So HPMCK15M also failed to control the drug release up to 12 hrs.

In this formulation HPMCK4M used to retard the drug release. As shown in the table 9 and fig. 2 HPMC K4M used in different percentages in F10, F11, F12, F13, F14, and F15 formulations. Started with 1% of polymer in F10, which shows burst release of drug, concentration is increased in order 3% in F11, 6.18% in F12, 9.2% in F13 and 12% in F14 which shows better control in drug release. In order to get exact optimization of drug release and to match with the inventor product the concentration of polymer is further increased to 15% which showed 91.2% drug released in 12hr. where complete erosion of matrix occurred. So this formulation was considered as optimized formulation.

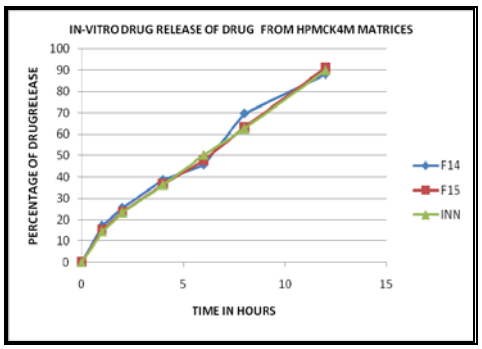

Fig. 3:*In-vitro* drug Release Profiles of Fluvoxamine (HPMC K4M) Matrice of F14, F15 and innovator kinetic analysis of disolution data

The release rate kinetic data for the F15 is shown in table 10, drug release data was best explained by zero order equation, as the plots showed the highest linearity (r^2 = 0.990), followed by Higuchi's equation (r^2 = 0.966) and Hixson-Crowell (r^2 = 0.915). As the drug release was best fitted in zero order kinetics, indicating that the rate of drug release is concentration in-dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the

distance for diffusion increases. The applicability of the formulation to the Hixson –Crowell cube root law indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time.

Table-10: Drug release kinetics of batch (F15) matrix tablets

Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
R^2	$K_0 (h^{-1})$	r^2	$K_1 (h^{-1})$	r^2	$K_H (h^{-1/2})$	R^2	$K_{HC} (h^{-1/3})$	r^2	n	$K_{KP} (h^{-n})$
0.990	7.191	0.904	-0.08	0.966	-22.78	0.915	1.473	0.808	0.45-0.89	0.827

*r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

Mechanism of drug release

The corresponding plot (log cumulative percent drug release vs log time) for the Korsmeyer-Peppas equation indicated a good linearity (r^2 = 0.808). The diffusion exponent "n" was between 0.45-0.89, which appears to indicating the diffusion mechanism is non-fickian diffusion. And indicates that the drug release was controlled by more than one process (both diffusion and dissolution).

CONCLUSION

Optimized formulation F15 (polymer percent15%) HPMC K4M has successfully controlled the drug release for 12 hours and the drug release pattern was good.

All the formulations were showed satisfactory flow properties, hardness, friability, content uniformity and release patterns. The dissolution data was positive and reveals the potential to formulate Fluvoxamine controlled release matrix tablets.

IR studies combined with stability studies proved the integrity of the developed matrix tablets.

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