ISSN: 2321-3760

Research Article

International Journal of Current Trends in Pharmaceutical Research

IJCTPR, 2014, Vol. 2(5): 621-627

www.pharmaresearchlibrary.com/ijctpr

Formulation and Evaluation of Fluoxetine Fast Dissolving Tablets

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Received: 06 June 2014, Accepted: 18 July 2014, Published Online: 15 September 2014

Abstract

The main aim of the present study was develop and evaluate the fast dissolving tablets of Fluoxetine by direct compression method. Sodium starch glycolate, Crospovidone and Croscarmellose sodium were used as super disintegrants to achieve the desired disintegration time required for the fast dissolving tablets. To mask the bitter taste and to improve the sweetness Peppermint flavor was used. Mannitol is used as a sugar based multifunctional diluent. The prepared tablets were evaluated for their physical (hardness, friability, weight variation) and all the parameters were found to be within the limits. Organoleptic (taste, mouth-feel, color) and functional (disintegration time) properties and for the drug content. The excipients were used in different concentrations. The release in the order of super disintegrants. Crospovidone > Croscarmellose > Sodium Starch Glycolate. The maximum *in vitro* dissolution was found to be with formulation F4. It clearly shows due to the superdisintegrant – (Crospovidone at 5%) and it seems to be the best.

Keywords: Fluoxetine, Sodium starch glycolate, Crospovidone and Croscarmellose sodium

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Manuscript ID: IJCTPR2234

PAPER-QR CODE

1. Introduction

The need for delivering drugs to patients efficiently and with few side effects has prompted pharmaceutical companies to engage in the development of new drug delivery system. A solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water is known as fast dissolving dosage form or mouth dissolving tablets [1]. When this type of tablet is placed into the mouth, the saliva will serve to rapidly dissolve the tablet. They are also known as oro-dissolving, rapid –dissolve oro-dispersible, melt in mouth, rapimelt, quick dissolving, fast melts, and porous tablets [2].

For treatment of depression various conventional oral dosage forms like tablets, capsules, oral suspension, syrups etc are available in market but the major drawbacks with these are many patients find it difficult to swallow (dysphagia) tablets and hard gelatin capsules. Dysphagia is a common problem encountered in all age groups in concern to solid dosage forms, which results in high incidence of non-compliance and ineffective therapy.

The difficulty experienced in particular by pediatrics and geriatrics patients. Other groups that may experience problems include the mentally ill, developmentally disable and patients who are uncooperative and hence do not take their medicines as prescribed leading to patient non-compliance. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance i.e., one, which will rapidly disintegrate in the mouth without need of water (fast dissolving tablet)[3, 4]. Advantages of this drug delivery system include administration without water, accuracy of dosage, easy portability, alternative to liquid dosage forms, ideal for pediatric and geriatric patients and rapid onset of action. Fluoxetine have become first line drug in the pharmacotherapy of patients with depression. This is because the drug possesses tolerability and safety advantages over the tricyclic agents. The concept of formulating or dispersible tablets containing fluoxetine offers a suitable and practical approach in serving desired objective of rapid disintegration and dissolution characteristics with increased bioavailability [5].

Criteria for Fast dissolving Drug Delivery System:

The tablets should [6]

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.

2. Materials and methods

Materials

Fluoxetine was a gift sample from Dr. Reedy's labs, Hyderabad, Crospovidone, Croscarmellose sodium, Sodium starch glycollate, Peppermint oil, CMC sodium, Sodium saccharin, Mannitol, Magnesium stearate and Talc were procured from SD Fine Chemicals, Mumbai, India. Double distilled water was used in entire study.

Methods

Preformulation studies:

Preformulation testing is the first step in the rationale development of dosage form of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined excipients. It gives extensive information to bring out good quality at high standard at which optimal dosage desired. Preformulation studies were performed on the drug (API), which included solubility and compatibility studies [8-12].

The following preformualtion studies were performed for Fluoxetine and excipients.

A. Determination of solubility

Solubility of Fluoxetine was performed in solvents like dichloromethane, dimethyl formamide, and dilute acids.

B. Calibration curve for Fluoxetine:

Accurately weighed 100 mg of Fluoxetine and added in 100 ml volumetric flask then it is diluted with 100ml of 0.1 N HCl to prepare stock solution of 1mg/ml and from this solution various concentrations are prepared and measure the absorbance by UV spectrophotometer at 225 nm.

Table 1: Calibration curve of Fluoxetine

Concentration	Absorbance
1	0.054
2	0.113
3	0.168
4	0.223
5	0.278
6	0.328
7	0.377

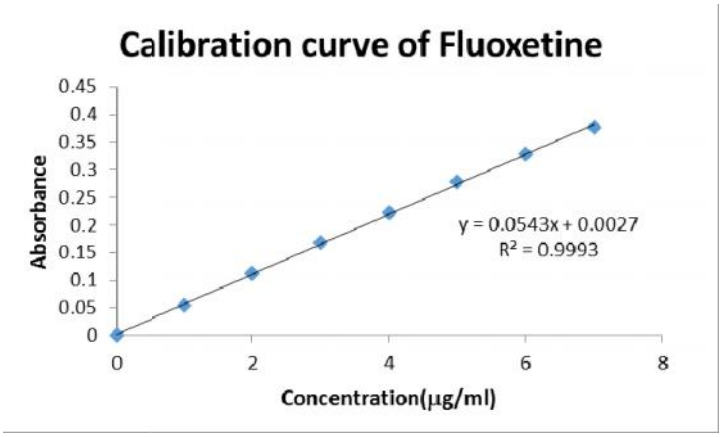

Figure 1: Calibration curve of Fluoxetine

C. Drug - excipients compatibility studies by FTIR:

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selections of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. FTIR spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug. In the preparation of the tablet formulation, drug and excipients may interact as they are in close contact with each other, which could lead to instability of the drug. Preformulation studies regarding the drug – excipients interaction are therefore very critical in selecting appropriate excipients. FTIR spectroscopy was employed to ascertain the compatibility between the Fluoxetine and the selected excipients.

Formulation of Fluoxetine fast dissolving tablets using various super disintegrates [12**]:**

a) Preparation of the tablets formulations by direct compression method:

Table 2: Formulation of Fluoxetine fast dissolving tablets

Ingredients(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Fluoxetine	400	400	400	400	400	400	400	400	400	40
Crospovidone	-	80	120	200	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	80	120	200	-	-	-
Sodium starch glycollate	-	-	-	-	-	-	-	80	120	200
Peppermint oil	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
CMC sodium	200	10	10	10	10	10	10	10	10	10
Sodium saccharin	40	02	02	02	02	02	02	02	02	02
Mannitol (g)	3.180	3.100	3.06	2.98	3.10	3.06	2.98	3.10	3.060	2.98
Magnesium stearate	80	04	04	04	04	04	04	04	04	04
Talc	100	05	05	05	05	05	05	05	05	05

Direct compression of powder:

Step-1:

Drug is sifted through sieve no 60. Required amounts super disintegrants are sifted through sieve no 80. Both are mixed together to for a homogeneous mixture.

Step-2:

Required amounts of all other excipient's except Magnesium stearate, Talc were sifted through sieve no 60 and the resultant mixture is treated with the mixture of above step and stored in desiccator. Magnesium stearate& Talc were added to the final mixture before compression.

Evaluation of Fluoxetine fast dissolving tablets:

A. Pre-compression parameters:

The quality of tablet is generally dictated by the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing step and all these can affect the characteristics of blends produced. The various characteristics of blends tested are as given below[13-18]:

Angle of Repose:

The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the powder and the Horizontal plane. If more powder is added to the pile,

it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

Tan θ = h/r

Therefore θ = Tan -1 h/r

Where

θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is the ratio of tapped density to bulk density. Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Carr's index:

Using poured bulk density and tapped bulk density the percentage compressibility of granules was determined, which is given as Carr's compressibility index.

$$\text{Carr's compressibility index (\%)} = \frac{\text{Tapped bulk density–poured bulk density}}{\text{Tapped bulk density}}$$

Table 3: Pre compression parameters

Formulation	Bulk density	Tapped Density	Carr's index	Angle of repose	Hausner ratio
F1	0.382	0.388	16.15	$27^{O}35^{l}$	1.001
F2	0.386	0.466	13.18	$28^{o}11^{l}$	1.120
F3	0.384	0.458	12.50	$29^{o}30^{l}$	1.115
F4	0.348	0.379	17.86	$29^{o}05^{l}$	1.148
F5	0.375	0.448	15.75	$27^{o}13l^{l}$	1.136
F6	0.380	0.486	14.57	$27^{o}30^{l}$	1.125
F7	0.326	0.400	15.86	$27^{o}55^{l}$	1.007
F8	0.352	0.394	13.45	$27^{o}30^{l}$	1.125
F9	0.376	0.418	18.75	$28^{o}25^{l}$	1.147
F10	0.425	0.489	16.36	$26^{o}19^{l}$	1.139

B. Post compression parameters:

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. hardness, friability, and In Vitro drug release studies.

Weight Variation test:

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation.

Measurement of tablet hardness:

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 3 tablets from each formulation was determined by Monsanto hardness tester.

Friability test:

It is measure of mechanical strength of tablets. Roche friabilator is used to determine the friability by following procedure. Tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, de dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (Initial weight-Final weight / Initial weight) X 100

Disintegration Time:

The USP device to test disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is positioned in 1 liter beaker of distilled water at37±2oC, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Table 4: Post compression evaluation of Fluoxetine fast dissolving tablets

Formulation	Weight Variation (%)	Hardness (kg/cm^2)	Friability test(%w/w)	Disintegration Time(sec)
F1	7.3±0.3	3.6±0.1	0.6±0.001	10±0. 2(min)
F2	7.0±0.4	3.5±0.02	0.5±0.002	6.98±0.2
F3	7.2±0.1	3.7±0.01	0.6±0.001	5.30±0.8
F4	7.4±0.2	3.9±0.02	0.8±0.002	5.10±0.3
F5	7.5±0.1	4.0±0.05	0.3±0.001	11.19±0.6
F6	7.2±0.1	3.8±0.04	0.4±0.003	14.15±0.4
F7	7.1±0.1	3.5±0.02	0.4±0.001	12.76±0.6
F8	7.3±0.2	3.5±0.03	0.5±0.001	25.35±0.9
F9	7.2±0.3	3.9±0.01	0.3±0.001	45.00±0.8
F10	7.2±0.1	3.5±0.01	0.5±0.002	60.00±1.2
All values were mentioned as mean ±S.D, Number of trials (n)=6				

***In Vitro* Dissolution studies:**

The dissolution test has been carried out for all the formulations. The in vitro drug release is performed using USP dissolution apparatus- II, 24 type paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37±0.5 0. 5 ml of the samples were withdrawn at predetermined time intervals of 0,10,20,40,60mins for a period of 60 min and replaced with the fresh medium of 0.1 N HCl. The samples were filtered through 0.45mm membrane filter, suitably diluted and analyzed at 225 nm using double beam UV/Visible spectrophotometer (Shimadzu Corporation, UV-1601, Japan). The content of drug was calculated using equation generated from standard calibration curve. The percentage release of Fluoxetine with respect to time for each batch.

Table 5: Comparison of percentage drug release of Fluoxetine Oro dissolving tablet

Time (min)	Percentage drug release (%)										
	Marketed	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0	0
10	68.55	20	83.45	83.65	90.12	71.55	80.98	82.98	68.52	67.52	67.35
20	69.35	32	84.65	84.32	90.37	71.65	83.16	85.59	68.62	676.84	65.05
40	69.39	45	86.48	88.45	96.05	72.54	85.45	86.5	69.51	68.34	66.35
60	75.45	60	88	89.54	99.15	75.98	85.65	87.95	73.95	72.55	68.98

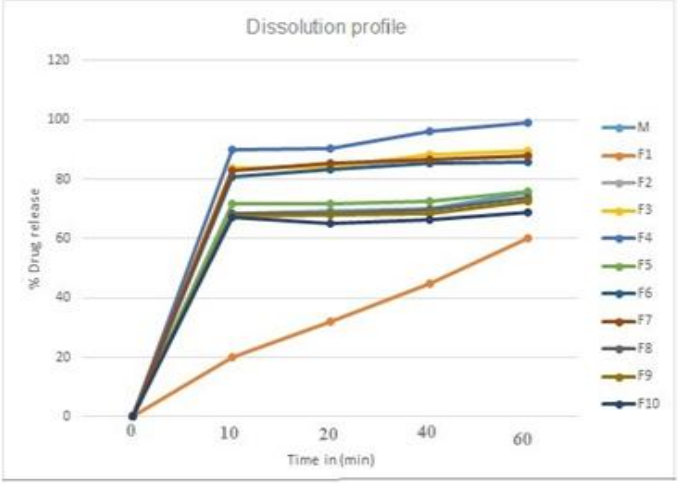

Figure 2: *In-vitro* dissolution profile of fluoxetine tablets

3. Results and Discussion

The powder was within the specific limit indicating good flow ability. With this the powder were found to be free flowing material and showed suitability to be compressed as tablets of expected weight. The results were shown in (Table 3). Thickness ranged from 5.18 – 5.22mm. Uniformity of weight was observed to be within the I.P. limits. Hardness was observed to be within the limit in the range of 3.5±0.02 to 4.0±0.05 except for control formulation the

hardness was found to be 4.5 kg/cm^2. Friability was observed between percent 0.3±0.001 to 0.8±0.002 % w/w hence within the limit of > 1%. Disintegration time was found to be between 10 -90 seconds. The recommended limit for fast dissolving tablets is that it should disintegrate within 3 minutes. Therefore, all formulations are within this limit and pass the test. The disintegration time (D.T) is higher for control (10 min) and for F4 it is only 5.10 seconds at (5%) and hence this was considered to be good compared to other formulations. The results were shown in (Figure 4).

In vitro dissolution test reveals the release increases from 60% to a maximum of almost 99.1%. The release is in the following order of super disintegrants: Crospovidone> Croscarmellose> Sodium Starch Glycolate. The maximum *in vitro* dissolution was found to be with formulation F4. The control formulation has the least *in vitro* dissolution (60 %) and the formulation F4 was found to contain maximum in vitro dissolution of 99.1%. It clearly shows due to the super disintegrant – (crospovidone at 5%) and it seems to be the best. The reason is its highly porous structure and water wicking mechanism into porous network of tablet and hence increases in concentration of crospovidone accounts for rapid drug release. The IR spectrum of fluoxetine shows us that there is no interaction between the drug and the excipient

4. Conclusion

The results have shown that Crospovidone5% as a superdisintegrant (F4) shows fastest disintegration (5.10sec) and maximum drug release (99.15%) within 20 minutes, when compared with other formulations. where formulation F4 has shown a marked increase in drug release profile when compared to that of control and other formulations. To conclude, Crospovidone at a concentration of 5% w/w is suitable for preparing fast dissolving tablet of fluoxetine because Crospovidone exhibits high capillary activity and pronounced hydration capacity with little tendency to gel formation.

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