International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 8, Issue 2, 2016

Original Article

FORMULATION AND EVALUATION OF ANTIDEPRESSANT ORODISPERSIBLE TABLETS

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Received: 25 Jan 2016, Revised and Accepted: 20 Mar 2016

ABSTRACT

Objective: Orodispersible tablet formulation was proposed to be developed for fluoxetine hydrochloride taking into consideration it's physical, chemical, pharmacological and pharmacokinetic properties and was proposed to be investigated with respect to its potential to be developed into novel drug delivery system

Methods: Carrying out pre-formulation studies such as drug-polymer interaction analysis by Fourier Transform Infrared (FTIR) spectroscopy and pre-compression characterization of a physical mixture of drug and excipients. Preparation of the orodispersible tablet by using various super disintegrants like croscarmellose, crospovidone & sodium starch glycolate. Preparation of the orodispersible tablet by using various methods like wet granulation method & sublimation method.

Results: To evaluate tablets for various physicochemical parameters such as hardness, friability, weight variation, drug content, wetting time, *in vitro* disintegration time, *in vitro* dissolution.

Conclusion: Finally concluded that the oro dispersible tablet of fluoxetine hydrochloride formulated by sublimation method by using crospovidone at 4.5% level used for depression treatment.

Keywords: Fluxetine, orodispersible tablets, Crosscarmellose, Crospovidone, Sodium starch glycolate

INTRODUCTION

The performance of ODTs depends on the technology used in their manufacture. The orally disintegrating property of these tablets is attributable to the quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration [1, 2]. Hence, the basic approaches to develop ODTs include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. Fluoxetine hydrochloride is the first agent of the class of antidepressants known as selective serotonin-reuptake inhibitors (SSRIs) [3]. Despite distinct structural differences between compounds in this class, SSRIs possess similar pharmacological activity.

MATERIALS AND METHODS

Materials

Fluoxetine, lactose, starch, aspartame, magnesium trisilicate, talc cross carmellose, crospovidone & sodium starch glycolate

Methods

For the following study, we are Taken captopril. Fluoxetine hydrochloride is the first agent of the class of antidepressants known as selective serotonin-reuptake inhibitors (SSRIs) [5-7]. In this study first, we did preformulation study.

In this preformulation study, we studied about the API characterization of drug, Drug-Excipient compatibility studies, Analytical method development, and Precompression parameters.

API characterization

It is necessary to study the physicochemical properties of the bulk drug-like physical appearance, solubility, melting point, particle size, and incompatibilities [4].

Analytical method development

It is studied for knowing about the purity of the drug. It is carried out by two methods HPLC or U. V. Here we have followed U. V method [9, 10]. Then we went for the formulation development.

Formulation development and evaluation

For this study, we developed 9 formulations in different ratio. The following table is shown formulation development for the present study.

Table 1: Formulation composition of orodispersible tablet of fluoxetine hydrochloride for wet granulation method

Ingredients	FW1 (mg)	FW2 (mg)	FW3 (mg)	FW4 (mg)	FW5 (mg)	FW6 (mg)	FW7 (mg)	FW8 (mg)	FW9 (mg)
Drug(Fluoxetine)	10	10	10	10	10	10	10	10	10
Lactose	59.5	58	56.5	59.5	58	56.5	59.5	58	56.5
Starch	20	20	20	20	20	20	20	20	20
Cross carmellose	1.5	3	4.5	-	-	-	-	-	-
Crospovidone	-	-	-	1.5	3	4.5	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	1.5	3	4.5
Poly vinyl pyrolidine	5	5	5	5	5	5	5	5	5
Aspartame	3	3	3	3	3	3	3	3	3
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table: 2 Formulation composition of orodispersible tablet of fluoxetine hydrochloride for sublimation method

Ingredients	FS1 (mg)	FS2 (mg)	FS3 (mg)	FS4 (mg)	FS5 (mg)	FS6 (mg)	FS7 (mg)	FS8 (mg)	FS9 (mg)
Drug(Fluoxetine)	10	10	10	10	10	10	10	10	10
Lactose	54.5	53	51.5	54.5	53	51.5	54.5	53	51.5
Starch	20	20	20	20	20	20	20	20	20
Camphor	5	5	5	5	5	5	5	5	5
Cross carmellose	1.5	3	4.5	-	-	-	-	-	-
Crospovidone	-	-	-	1.5	3	4.5	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	1.5	3	4.5
Poly vinyl pyrollidine	5	5	5	5	5	5	5	5	5
Aspartame	3	3	3	3	3	3	3	3	3
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

RESULTS AND DISCUSSION

Standard graph of Fluoxetine hydrochloride in 0.1N HCl

Table: 3 Data of the standard calibration curve of fluoxetine hydrochloride, Medium 0.1N HCl; λ_{max}=226 nm

Concentration (µg/ml)	Absorbance at 226 nm
0	0
2	0.066
4	0.186
6	0.242
8	0.333
10	0.418
12	0.505
14	0.582
16	0.669
18	0.757
20	0.836

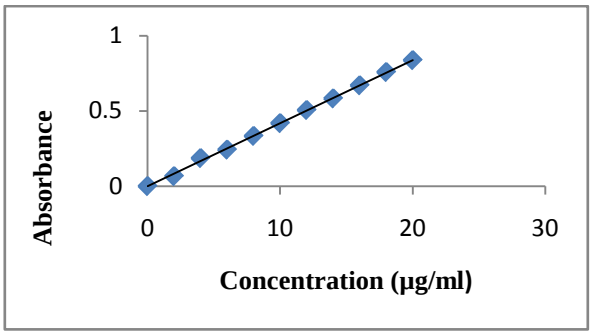


Fig. 1: Standard graph of fluoxetine hydrochloride. Medium 0.1N HCl; λ_{max}=226 nm

Preformulation studies

Fourier transforms infrared spectroscopy (FTIR)

Table 4: Observed frequencies in the FTIR spectra of pure drug (fluoxetine hydrochloride) and physical mixture with their assignments

Frequency observed in IR spectrum (cm^{-1})	Assignments
3440.7	Amines stretching vibration (N-H)
1070.1	(N-C) stretching
2960.3	Alkane (C-H stretching)
3014.5	Aromatic (C-H stretching)
1518.2	(C=C stretching)
1242	Phenoxy stretching vibration (C-O-Aromatic group)
1331	Halide stretching vibration (C-F)
1108	Fingerprint absorption bands
1050	
842	
699	
588	
526	

Powder characterization

The powder mixtures of different formulations were evaluated for angle of repose, Hausner ratio, and compressibility index and their values were shown in (table 6, 3).

Evaluation of tablets

The Oro dispersible tablets of different formulations were evaluated for Weight variation, Hardness, Thickness, Friability test, Drug content and their values were shown in (table 6, 4).

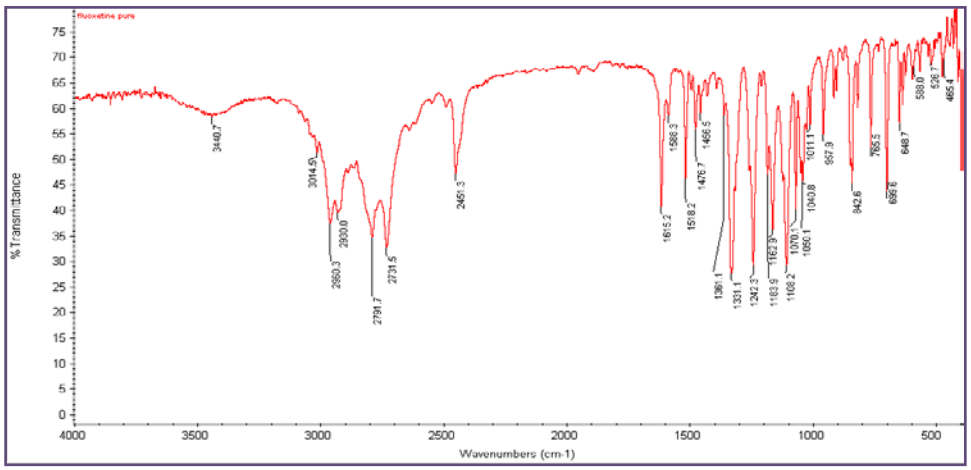


Fig. 2: FTIR spectra of fluoxetine hydrochloride. (Pure drug)

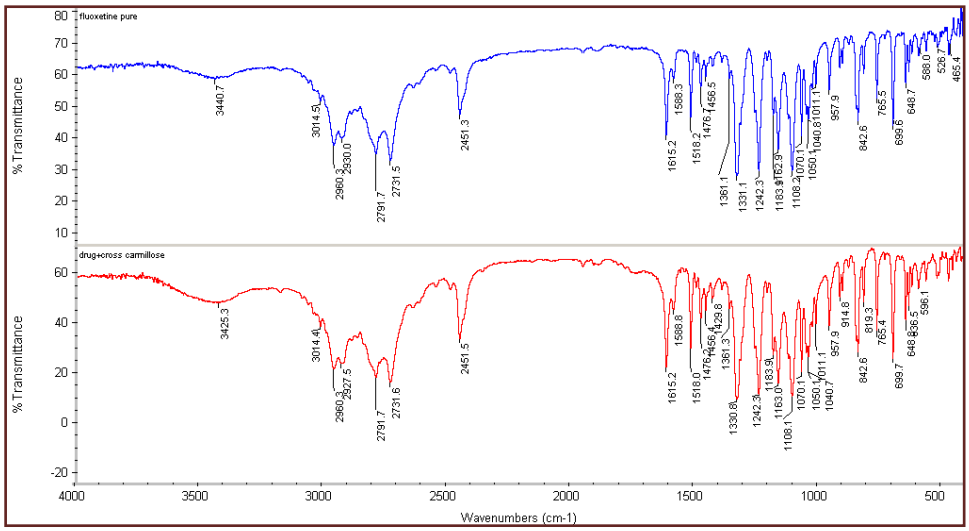


Fig. 3: FTIR spectra of physical mixture containing drug and Cross carmellose

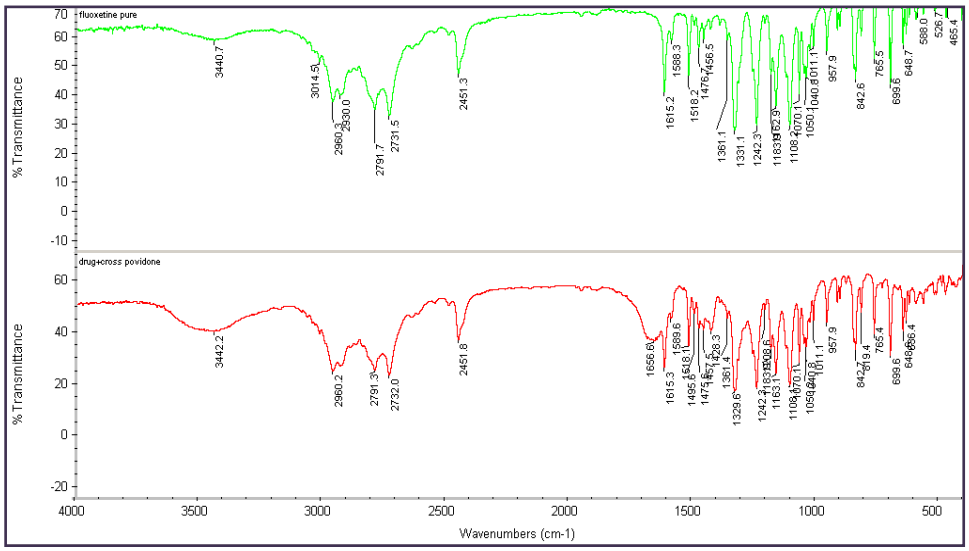


Fig. 4: FTIR spectra of physical mixture containing drug and Cross povidone

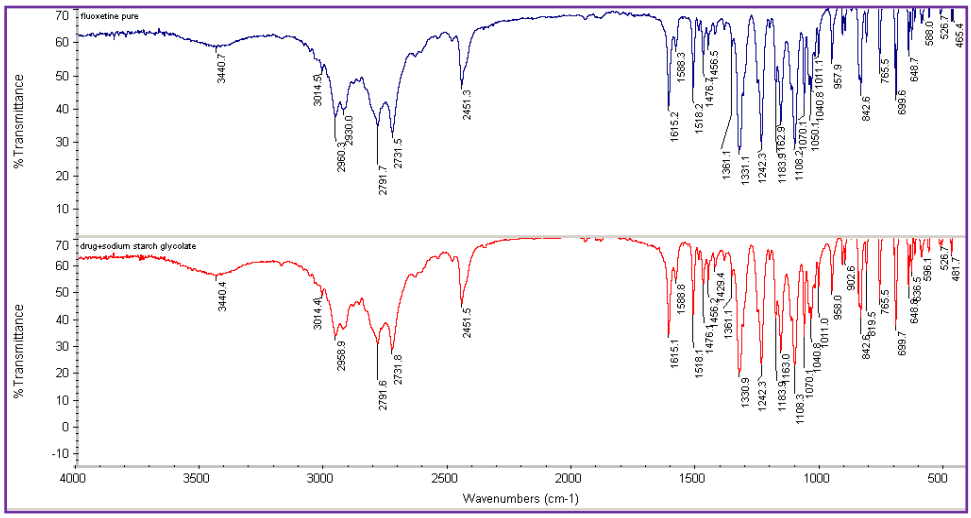


Fig. 5: FTIR spectra of physical mixture containing drug and Sodium starch glycolate

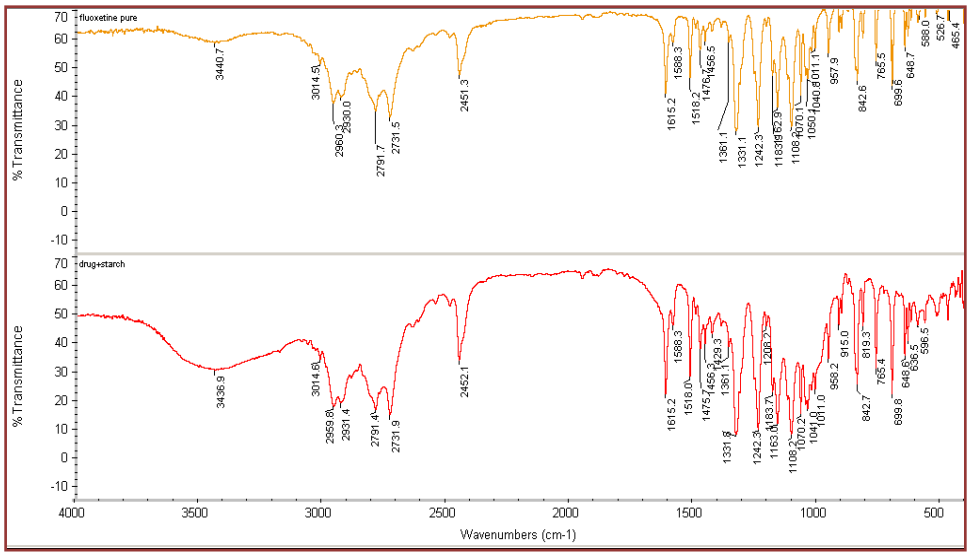


Fig. 6: FTIR spectra of physical mixture containing drug and starch

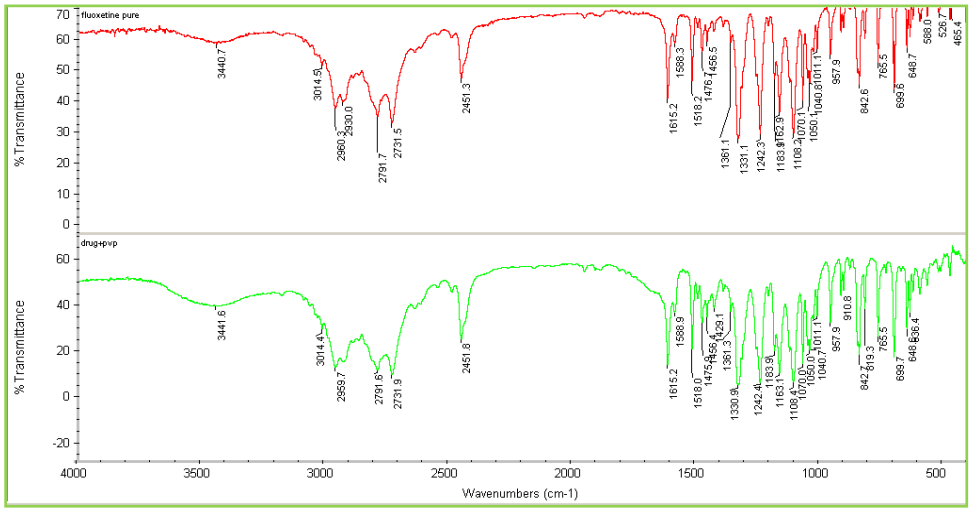


Fig. 7: FTIR spectra of physical mixture containing drug and PVP

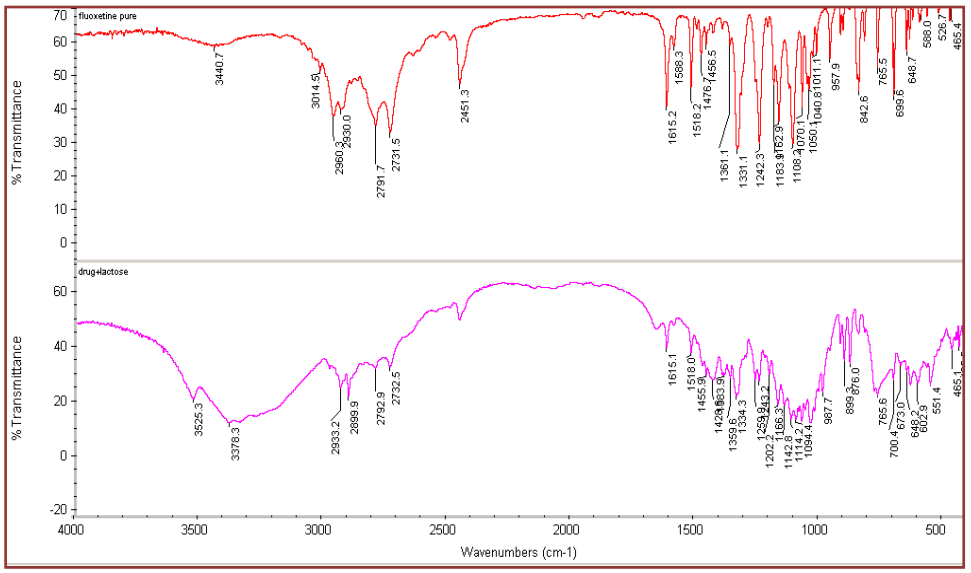


Fig. 8: FTIR spectra of physical mixture containing drug and lactose

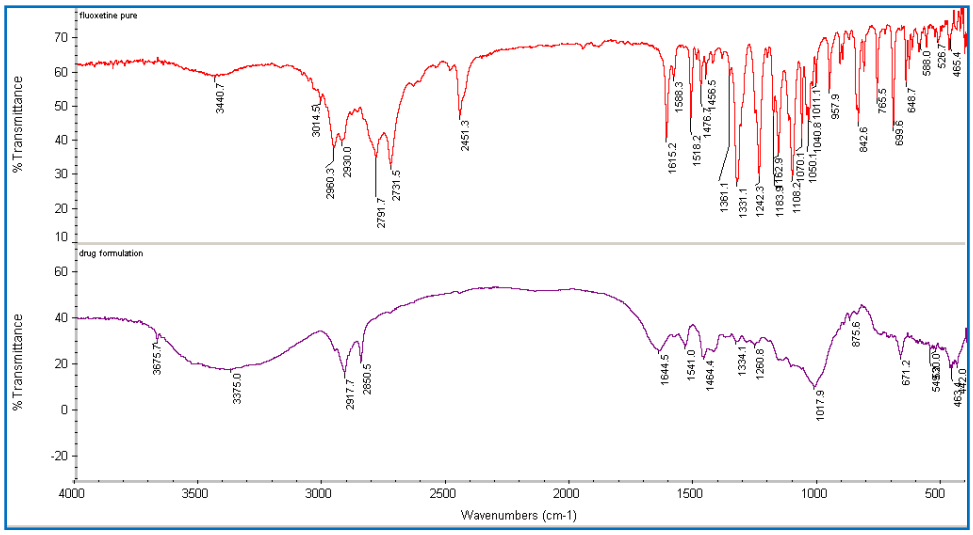


Fig. 9: FTIR spectra of drug formulation

Table 5: Flow properties of the final powder blend

Formula code	Bulk density (gm/cm³)	Tapped density(gm/cm³)	Carss index (%)	Angle of repose	Hausners ratio
FW1	0.341±0.04	0.422±0.04	12.46±1.87	27 °.11′±0.065	1.14±0.01
FW2	0.357±0.03	0.423±0.06	9.50±1.23	26 °.12′±0.043	1.10±0.03
FW3	0.365±0.12	0.405±0.06	12.75±1.98	28 °.21′±0.032	1.14±0.01
FW4	0.333±0.32	0.403±0.02	11.11±0.05	28 °.32′±0.05	1.12±0.03
FW5	0.371±0.05	0.417±0.05	13.08±0.42	27 °.09′±0.06	1.15±0.02
FW6	0.370±0.06	0.467±0.09	12.69±0.05	29 °.12′±0.03	1.15±0.03
FW7	0.364±0.06	0.467±0.16	10.61±0.76	27 °.34′±0.07	1.14±0.06
FW8	0.369±0.09	0.428±0.14	10.73±0.32	30 °.20′±0.04	1.11±0.02
FW9	0.375±0.05	0.408±0.31	12.55±0.64	26 °.10′±0.08	1.12±0.03
FS1	0.378±0.01	0.403±0.87	11.21±0.46	27 °.22′±0.03	1.14±0.05
FS2	0.339±0.07	0.402±0.54	11.81±0.97	27 °.31′±0.03	1.17±0.06
FS3	0.357±0.12	0.413±0.07	12.09±0.97	28 °.08′±0.07	1.13±0.03
FS4	0.378±0.14	0.427±0.34	9.95±0.13	29 °.32′±0.07	1.12±0.02
FS5	0.369±0.15	0.431±0.24	11.13±0.1	31 °.41′±0.08	1.08±0.01
FS6	0.381±0.21	0.418±0.65	11.28±1.09	29 °.28′±0.09	1.12±0.02
FS7	0.384±0.06	0.422±0.06	11.57±1.65	28 °.21′±0.04	1.21±0.05
FS8	0.344±0.25	0.413±0.07	11.75±0.05	29 °.08′±0.03	1.32±0.02
FS9	0.362±0.14	0.395±0.03	12.53±0.06	27 °.11′±0.05	1.14±0.05

Data represents mean±SD (n=3)

Table 6: Physical evaluation parameters of orodispersible tablets

Formula code	Weight variation(mg)	Hardness (Kg/cm²)	Thickness (mm)	Friability (%)	Drug content (%)
FW1	99.4±0.6	3.1±0.1	2.20±0.01	0.41±0.03	95.9±0.07
FW2	98.9±0.81	3.2±0.12	2.22±0.03	0.57±0.04	98.6±0.06
FW3	100.05±0.85	3.3±0.15	2.23±0.035	0.47±0.02	98.1±0.05
FW4	99.6±0.37	3.1±0.13	2.12±0.03	0.34±0.035	97.6±0.02
FW5	100.3±0.53	3.2±0.14	2.20±0.015	0.42±0.03	97.8±0.07
FW6	99.5±0.97	3.4±0.1	2.11±0.03	0.35±0.015	99.1±0.02
FW7	100.3±0.88	3.2±0.17	2.28±0.035	0.46±0.034	95.4±0.04
FW8	99.7±0.51	3.1±0.1	2.30±0.03	0.57±0.015	96.4±0.05
FW9	98.8±0.88	3.2±0.15	2.29±0.04	0.66±0.026	97.1±0.052
FS1	99.5±1.08	2.5±0.21	2.34±0.052	0.62±0.04	96.4±0.041
FS2	100.4±0.65	2.7±0.16	2.37±0.05	0.59±0.05	98.6±0.039
FS3	100.7±1.07	3.0±0.1	2.49±0.05	0.55±0.03	97.1±0.05
FS4	98.8±1.23	2.8±0.2	2.25±0.036	0.5±0.026	99.1±0.045
FS5	99.2±0.19	2.7±0.21	2.31±0.03	0.54±0.03	98.1±0.061
FS6	98.7±0.89	3.1±0.32	2.24±0.07	0.44±0.032	98.3±0.042
FS7	100.3±1.21	2.7±0.08	2.45±0.06	0.61±0.03	96.9±0.061
FS8	98.01±1.46	2.8±0.16	2.51±0.03	0.65±0.04	97.6±0.04
FS9	100.3±0.78	2.7±0.17	2.49±0.04	0.61±0.031	97.8±0.05

Data represents mean±SD (n=3)

Disintegration time

The Orodispersible tablets of disintegration time were evaluated, and their values were shown in (table.6.5. and in fig. 6.10).

Table 7: Disintegration times of orodispersible tablets

Formula code	Disintegration time (sec)
FW1	86±4.35
FW2	76±2.51
FW3	72±1.5
FW4	75±1.4
FW5	43±1.15
FW6	35±3.6
FW7	106±4.09
FW8	97±3.6
FW9	86±3.65
FS1	64±4.5
FS2	45±2.51
FS3	41±2
FS4	25±3.05
FS5	20±1.08
FS6	13±1.5
FS7	86±3.7
FS8	74±4.3
FS9	65±3.6

Data represents mean±SD (n=3)

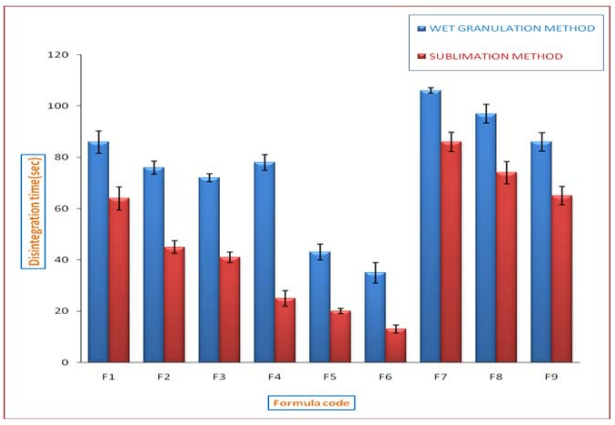


Fig. 10: Disintegration time profile of orodispersible tablets

Wetting time

Wetting time of dosage form is related to the contact angle. The Orodispersible tablets of disintegration time were evaluated, and their values were shown in (table.6.6. and in fig. 6.11 and 6.12).

Table 8: Wetting time of orodispersible tablets

Formula code	Wetting time (sec)
FW1	82±2.3
FW2	71±3.1
FW3	65±2.45
FW4	59±3.54
FW5	38±4.12
FW6	30±1.23
FW7	94±5.2
FW8	89±3.21
FW9	80±1.8
FS1	51±1.32
FS2	40±1.42
FS3	37±1.23
FS4	23±1.54
FS5	16±2.32
FS6	10±1.23
FS7	75±1.24
FS8	65±1.45
FS9	54±2.34

Data represents mean±SD (n=3)

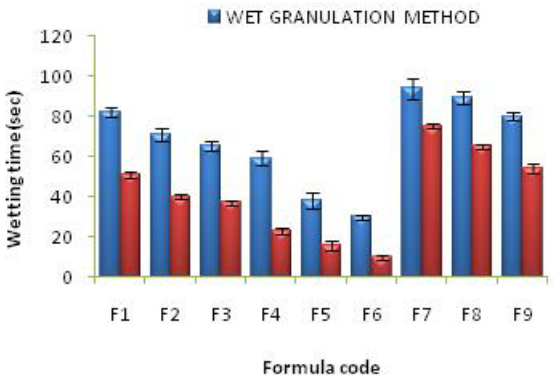
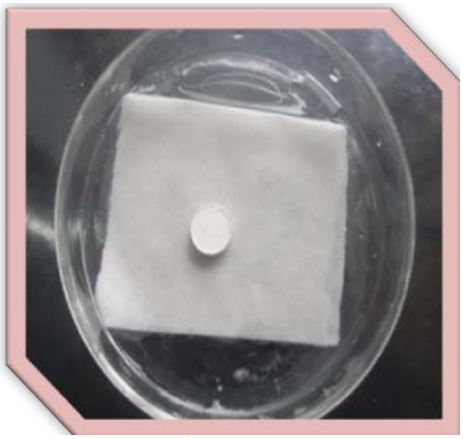


Fig. 11: Wetting time profile of orodispersible tablets



Before wetting

After wetting

Fig. 12: Photograph of wetting of oro dispersible tablets

***In vitro* dissolution studies**

Table 9: Cumulative percent drug release of formulation with cross carmellose as super disintegrant. Medium= 0.1N HCl, λ_{max}=226 nm

Time(min)	FW1	FW2	FW3
5	51.5±0.87	53.3±0.98	57.1±0.57
10	58.3±0.77	60.3±1.04	64.5±0.98
15	67.2±0.98	71.4±0.82	72.3±0.67
20	73.4±1.07	76.3±1.18	79.3±1.67
30	79.3±0.89	81.3±0.87	85.9±1.34
45	82.3±1.06	84.3±0.73	88.5±0.98
60	85.2±0.75	87.5±0.65	91.5±0.85

Data represents mean±SD (n=3)

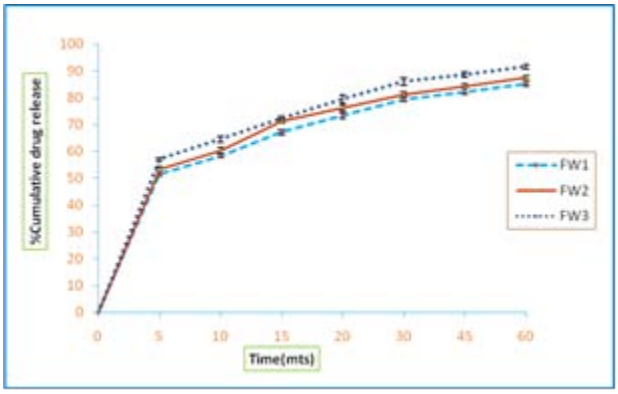


Fig. 13: Cumulative % drug release of orodispersible tablets incorporated with cross carmellose Vs Time, Medium= 0.1N HCl, λ_{max}=226 nm

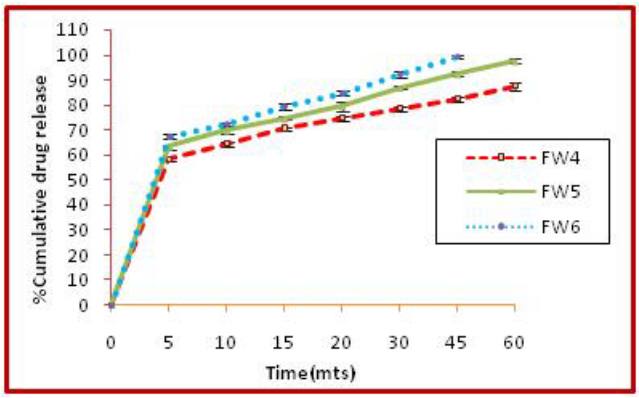


Fig. 14: Cumulative % drug release of orodispersible tablets incorporated with Crospovidone Vs Time, Medium= 0.1N HCl, λ_{max}=226 nm

Table 10: Cumulative percent drug releases of formulations with Crospovidone as super disintegrant. Medium= 0.1N HCl, λ_{max}=226 nm

Time(min)	FW4	FW5	FW6
5	58.1±0.87	63.2±0.97	67.5±0.87
10	64.4±0.93	69.7±1.38	72.3±0.53
15	70.5±0.65	74.7±0.67	79.6±1.25
20	74.5±0.98	79.4±1.67	84.5±0.76
30	78.3±1.07	86.8±0.65	92.3±1.38
45	82.1±0.89	92.3±0.98	99.4±0.67
60	87.3±1.46	97.5±0.77	-

Data represents mean±SD (n=3)

Table 11: Cumulative percent drug releases of formulations with sodium starch glycolate as super disintegrant. Medium= 0.1N HCl, λ_{max}=226 nm

Time (min)	FW7	FW8	FW9
5	50.8±0.97	52.5±1.53	56.3±1.65
10	57.3±0.87	59.5±0.65	62.8±0.98
15	65.5±1.03	68.3±0.97	71.4±0.47
20	71.6±0.63	75.8±0.76	78.3±1.42
30	77.4±0.99	80.3±1.45	82.6±0.95
45	80.6±1.42	83.1±0.63	85.9±0.86
60	83.4±0.86	86.8±0.99	90.4±1.45

Data represents mean±SD (n=3)

Table 12: Cumulative percent drug releases of formulations with Cross carmellose as super disintegrant, Medium= 0.1N HCl, λmax=226 nm

Time (min)	FS1	FS2	FS3
5	60.3±0.43	64.3±0.64	67.5±0.83
10	68.6±0.93	70.9±0.46	71.7±0.93
15	73.6±1.36	76.3±0.82	78.3±0.78
20	78.4±0.75	80.2±0.93	85.9±0.63
30	81.3±0.78	85.6±0.62	91.3±1.26
45	87.5±0.86	92.4±0.87	99.3±0.73
60	94.1±0.93	99.1±1.07	-

Data represents mean±SD (n=3)

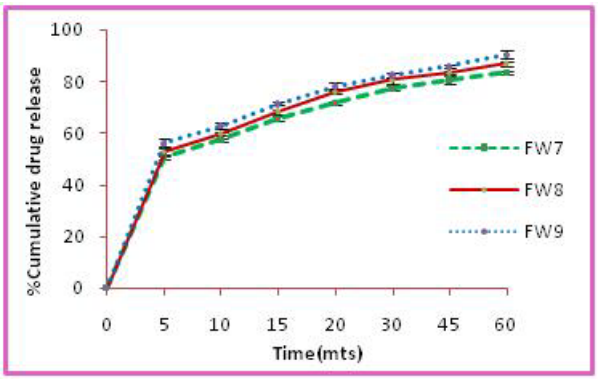


Fig. 15: Cumulative % drug release of orodispersible tablets incorporated with sodium starch glycolate Vs Time, Medium= 0.1N HCl, λ_{max}=226 nm

The oro dispersible tablets prepared by sublimation method FS-1 to FS-9 by using super disintegrates were evaluated for *in vitro* drug release behavior, and the results of the formulations were expressed in (tables 6.10-6.12).

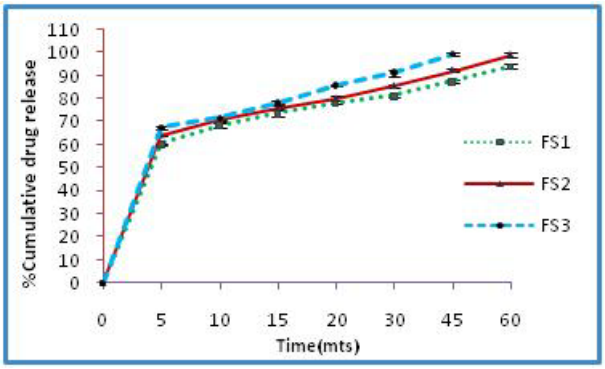


Fig. 16: Cumulative % drug release of orodispersible tablets incorporated with cross-carmellose Vs Time, Medium= 0.1N HCl, λ_{max}=226 nm

Table 13: Cumulative percent drug releases of formulations with Cross povidone as super disintegrant, Medium= 0.1N HCl, λ_{max}=226 nm

Time (min)	FS4	FS5	FS6
5	69.8±0.88	72.3±0.72	78.9±0.91
10	75.7±0.93	80.3±0.67	89.3±0.85
15	78.6±0.76	88.7±0.94	99.5±0.95
20	81.3±0.83	95.4±0.76	-
30	88.6±0.67	98.9±1.12	-
45	92.4±1.04	-	-
60	99.3±0.95	-	-

Data represents mean±SD (n=3)

Table 14: Cumulative percent drug releases of formulations with sodium starch glycolate as super disintegrant, Medium= 0.1N HCl, λ_{max}=226 nm

Time (min)	FS7	FS8	FS9
5	59.8±0.96	61.4±1.07	65.3±0.84
10	65.8±0.45	67.3±0.87	70.4±0.73
15	71.9±1.13	74.8±0.97	78.3±0.67
20	77.6±0.99	78.8±0.87	83.2±0.68
30	80.4±0.82	84.9±0.73	90.5±0.56
45	85.3±0.95	90.3±0.75	98.9±0.86
60	92.5±0.86	96.3±0.98	-

Data represents mean±SD (n=3)

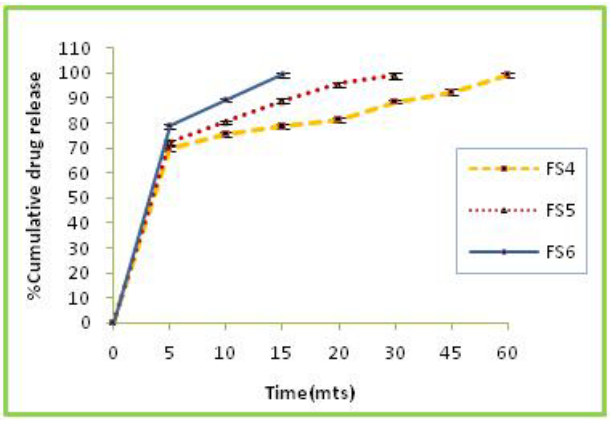


Fig. 17: Cumulative % drug release of orodispersible tablets incorporated with Cross povidone Vs Time, Medium= 0.1N HCl, λ_{max}=226 nm

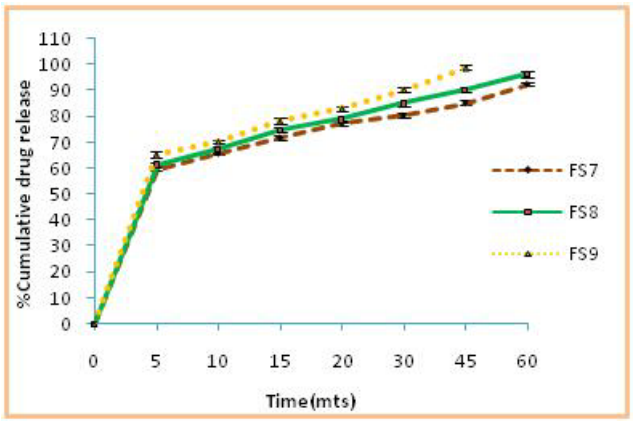


Fig. 18: Cumulative % drug release of orodispersible tablets incorporated with sodium starch glycolate Vs Time, Medium= 0.1N HCl, λ_{max}=226 nm

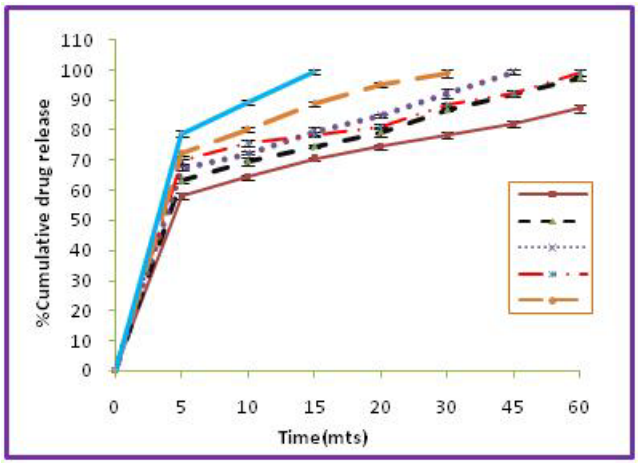


Fig. 19: Comparison of cumulative % drug release of oro dispersible tablets incorporated with Cross povidone Vs Time, Medium= 0.1N HCl, λ_{max}=226 nm

Model fitting data for drug release

Table 15: Kinetic model fitting data for all the formulations prepared by wet granulation method

Batch	Zero order	First order
FW1	0.820	0.913
FW 2	0.794	0.913
FW 3	0.823	0.941
FW 4	0.894	0.971
FW 5	0.938	0.984
FW 6	0.958	0.986
FW 7	0.831	0.918
FW 8	0.811	0.917
FW 9	0.838	0.952

Table 16: Kinetic model fitting data for all the formulations prepared by sublimation method

Batch	Zero order	First order
FS1	0.921	0.976
FS2	0.956	0.997
FS 3	0.951	0.981
FS 4	0.964	0.989
FS5	0.910	0.982
FS6	0.991	**0.998**
FS7	0.918	0.972
FS 8	0.926	0.974
FS 9	0.961	0.931

CONCLUSION

Oro dispersible tablet of fluoxetine hydrochloride prepared using various concentrations (1.5%, 3% & 4.5%) of super disintegrates like crosscarmellose, crospovidone, sodium starch glycolate by wet granulation method & sublimation method. The preformulation studies by FTIR confirmed no interactions between drug and polymers. The prepared formulations were evaluated for the pre-compression parameters & the values were within prescribed limits and indicated good free flowing properties. The physical parameters were found satisfactory & within the limits. Upon comparison sublimation method was showed good results for disintegration time, wetting time & *in vitro* drug release studies because sublimation of camphor to increase the porosity of the tablets. The tablets prepared with crospovidone at 4.5% concentration (FS-6) by sublimation method was found to be best formulation as it exhibited satisfactory physical parameters, least disintegration time (13 sec.),wetting time (10 sec.) & highest % drug release (99.5%) in 15 min. The drug release pattern from the optimized formulations was best fitted to first-order kinetics.

AKNOWLDGEMENT

We would like to thank our Director sir and other teaching and nonteaching faculty who help to carry out this research in the institution.

CONFLICT OF INTERESTS

Declare none

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