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Original Article

Comparsion Study of Effect of Superdisintegrant S on Formulation and Evaluation of Fluoxetine Hydrochloride Orodispersible Tablets by Wet Granulation and Sublimation Method

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ABSTRACT

The purpose of this research was to investigate the efficiency of superdisintegrants such crosscarmellose sodium, cross povidone and sodium starch glycolate in formulating orodispersible tablets of Fluoxetine Hydrochloride tablets. Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor drug which is used in psychiatric disorder like depression. The efficiency of three super disintegrants were investigated by wet granulation and sublimation method with different concentratioins of 1.5%, 3% and 4.5%. 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 tablets prepared by wet granulation & sublimation method were evaluated for physical parameters, wetting time, disintegration time, content uniformity and in vitro dissolution. The physical parameters were found to be 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 increases 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%) at 15 mins. In order to determine the mode of release, the data was fitted into various kinetic models and the optimized formulation followed first order kinetics.

Keywords: Orodispersible tablet, Fluoxetine hydrochloride, Wet granulation method, Sublimation method, Super disintegrants, FTIR analysis.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. One important drawback of solid dosage forms for some patients is difficult to swallow (Paediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms) (Indurwade NH -2002)[1] hence our research regarding orodispersible tablets can overcome the problem.

The novel technology of oral disintegrating dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick dispersible tablets. 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. 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. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. These volatile materials are then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents[2,3,4,5].

Fluoxetine (D. Indumati 2011) 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 orodispersible tablets containing fluoxetine offers a suitable and practical approach in serving desired objective of rapid disintegration and dissolution characteristics with increased bio-availability.

MATERIALS AND METHODS

Fluoxetine Hydrochloride is obtained from aurobindo pharma Pvt Ltd., Aspartame is obtained from Elvina Pharmaceutical, Mumbai., Sodium starch glycolate, cross povidone, crosscarmellose sodium are obtained from Dr. Reddy's laboratories, Hyderabad., lactose, pvpk-30, magnesium stearate, talc and camphor all were obtained from Sd fine chemicals Mumbai.

Preparation of orodispersible tablets

Preparation of fluoxetine hydrochloride orodispersible tablets by Wet granulation method

Fluoxetine hydrochloride raw material and all excipients were passed through sieve no. #60 before granulation and lubrication. The required quantity of fluoxetine hydrochloride and other excipients (except lubricants and glidants) were weighed and mixed uniformly. Then the mixture was made to a damp mass using methanol. Then the prepared mass was passed through sieve no. #16. The prepared granules were dried in an oven at a temperature of 50^{o}C for one hour.

The granules obtained were lubricated by adding and mixing with talc, magnesium stearate and colloidal silicon dioxide. The lubricated granules were evaluated and punched into tablets with an average weight of 100 mg; using Cadmach tabletting machine. Nine formulations were prepared (Indumati 2011). The composition of formulations is shown in (Table 1)

Preparation of Fluoxetine hydrochloride orodispersible tablets by Sublimation method

Orodispersible tablets of Fluoxetine hydrochloride were prepared using camphor as subliming agent. Sodium starch glycolate, crosscarmellose and cross povidone as superdisintegrants. Each of the super-disintegrants were used in three different concentrations of 1.5%, 3% and 4.5%. All the ingredients were passed through mesh screen no. #60 and weighed in geometrical order. All the materials were directly compressible so this uniformly mixed blend was compressed into tablets using single tablet punching machine (cadmach). Sublimation was performed from tablets by keeping in hot air oven at 60ºC for 1 hour. Nine formulations were prepared (S. A. Desai-2006). The composition of formulations is shown in (Table.2).

RESULTS AND DISCUSSION

The present study was aimed to study the effect of superdisintegrants on development of fluoxetine orodispersible tablet by wet granulation and sublimation method. The formulation compositions of all the tablets are shown in (Table.1, 2). The formulations FW1-FW9 was prepared by wet granulation method and the formulations FS1-FS9 prepared by sublimation method. The orodispersible tablets were prepared with super disintegrates like cross-carmellose, crospovidone & sodium starch glycolate in varying amounts.

Prepared granules were subjected for FTIR studies and from the spectra it was observed that observed frequencies in the FTIR spectra of pure drug showing in (Fig No. 1) remained same in the spectra obtained using formulation mixture, which shows that there were no interaction of the drug with the other excipients. And also the prepared granules were subjected for both pre and post compressional parameters all the results were found to be within the prescribed limits which were shown in table no 3 and table no. 4.

Disintegration time

Disintegration time for orodisperible prepared by wet granulation and sublimation method containing cross-carmellose as super disintegrant in the concentration range 1.5%, 3%, &4.5% was found to be 86±4.35, 76±2.51,& 72±1.5 sec of wetgranulation and 64±4.5, 45±2.5 & 41±2 sec sublimation method respectively. Similarly for cross povidone as super disintegrant in the concentration range 1.5%, 3%, &4.5% was found to be 75±1.4, 43±1.15, & 35±3.6 sec and 25±3.05, 20±1.08, & 13±1.5 sec respectively. Similarly for sodium starch glycolate as super disintegrant in the concentration range 1.5%, 3%, &4.5% was found to be 106±4.09, 97±3.6, & 86±3.65sec and 86±3.7, 74±4.3,& 65±3.6 sec respectively. From these results the least disintegration time of 35±3.6 sec. was obtained in tablets prepared by wet granulation method and 13±1.5 sec by sublimation method with 4.5% concentration of cross povidone as a super disintegrant and the results were shown in fig no:2. The probable reason is that it might be due to solvent intake in to the matter by capillary action. The order of disintegration time by both wet granulation and sublimation method follows cross povidine > Cross carmellose > Sodium starch glycolate and the results were shown in fig no. 2

Wetting time

Wetting time for the orodispersible tablets prepared by wet granulation and sublimation method containing cross-carmellose as superdisintegrant in the concentration range 1.5%, 3%, &4.5% was found to be 82±2.3, 71±3.1, & 65±2.45sec for wetgranulation and for sublimation 51±1.32, 40±1.42, & 37±1.23 sec respectively. Similarly for cross povidone as super disintegrant in the concentration range 1.5%, 3%, &4.5% was found to be 59±3.54, 38±4.12, & 30±1.23 sec and 23±1.54, 16±2.32, & 10±1.23 sec respectively. Similarly for sodium starch glycolate as super disintegrant in the concentration range 1.5%, 3%, &4.5% was found to be 94±5.2, 89±3.21, & 80±1.8 sec and 75±1.24, 65±1.45,& 54±2.34 sec respectively. The order of wetting time of least wetting time for both the methods include is cross povidine > Cross carmellose > Sodium starch glycolate.

By comparison of these two methods the tablets prepared by sublimation method showed lesser wetting time than the wet granulation method. The least wetting time was observed in the formulation FS6 (Because the tablet having porous matrix due to sublimation of camphor) which ishaving 4.5 % cross carmellose as super disintegrant prepared by sublimation method value was found to be 10±1.23sec. and the results were shown in fig no. 3

In Vitro Dissolution Studies

In vitro dissolution study of orodispersible tablets prepared by wet granulation an method incorporated with cross carmellose as super disintegrant in 1.5%, 3% & 4.5% and the percent of drug release from formulations FW1, FW2 & FW3 was observed to be 85.2±0.75, 87.5±0.65 and 91.5±0.85 in 60 mins and FS-1, FS-2 & FS-3 90.2±0.75, 93.4±0.65 and 96.5±0.85 in 60 mins respectively and the percent of drug release was calculated. The results indicated that with increase polymer concentrations, drug release was also increased respectively. Similarly formulations prepared by cross povidone as super disintegrant in 1.5%, 3% & 4.5% concentration coded as FW-4, FW-5 & FW-6 was observed to be 87.3±1.46, 97.5±0.77 in 60 mins where as FW-6 showed 99.4±0.67 percent of drug release up to 45 minutes where as incase of sublimation process FS-6 has maximum drug release (99.5±0.95%) up to 15mts, FS-5 at 30mts shown 98.9±1.12% and FS-4 at 60mts shown 99.3±0.95%. Similarly formulations FW-7, FW-8 & FW-9 was observed to be 83.4±0.86, 86.8±0.99 and 90.4±1.45 in 60 mins and for FS-9 has maximum drug release (98.9±0.86%) up to 45 mts, FS-8 at 60 mts shown 96.3±0.98% and FS-7 at 60 mts shown 92.5±0.86%. respectively.

It was finally concluding that with all the above formulations prepared by using the superdisintegrant crospovidone in concen-trations were used 1.5%, 3%, and 4.5% in wet granulation method (FW4-FW6) & in sublimation method (FS4-FS6) results showed in fig no 4 that the FS-6 having more % drug release than the all other formulation up to 15mts about 99.5% drug released. Because in the wet granulation method the particles are more adhered and having more attraction forces, such that the disintegration time is more compared to sublimation method & drug released is decreased. But in sublimation method the porous matrix is formed due to sublimation of camphor results the water easily intake and with less bonding between the particles, readily disintegrate & the drug release also more.

Hence the orodispersible tablet of fluoxetine hydrochloride formulated by sublimation method by using crospovidone at 4.5% level used for depression treatment.

Model fitting data for drug release

The mechanism of release for all the formulations was determined by finding the

R^2 value for each kinetic model viz. Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations shown in table no 5. Therefore the most probable mechanism that optimized formulation follows the release patterns first order knetics followed by non-fickian diffusion or anomalous diffusion.

CONCLUSION

In the present study the disintegrating properties of the crosscarmellose sodium, Crospovidone and Sodium starch glycolate had been studied. All the disintegrants showed a rapidly disintegration, which is required for faster drug dissolution and improved bioavailability. Overall, the results suggest that convenience of formulation of orodispersible tablets of fluoxetine containing Cross povidone P (polyplasdone XL) as a super disintegrant for both the wet granulation and sublimation technique. Finally the optimum selected formula has satisfactory physical resistance, fast Invitro disintegration time, faster dissolution rate, and noincompatibility problems.

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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

Table 3. Evaluation of Pre-compressional parameters

Formula code	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	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 4. Evaluation of Pre-compressional parameters

Formula code	Weight variation(mg)	Hardness (Kg/cm^2)	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)

Table 5. Evaluation of Pre-compressional parameters

Batch	Zero order	First order	Higuchi	Peppas	n value
FW 4	0.894	0.971	0.966	0.992	0.162
FW 5	0.938	0.984	0.990	0.995	0.179
FW 6	0.958	0.986	0.991	0.980	0.184
FS 4	0.964	0.989	0.992	0.979	0.139
FS5	0.910	0.982	0.964	0.981	0.185
FS6	0.991	0.998	0.995	0.987	0.207

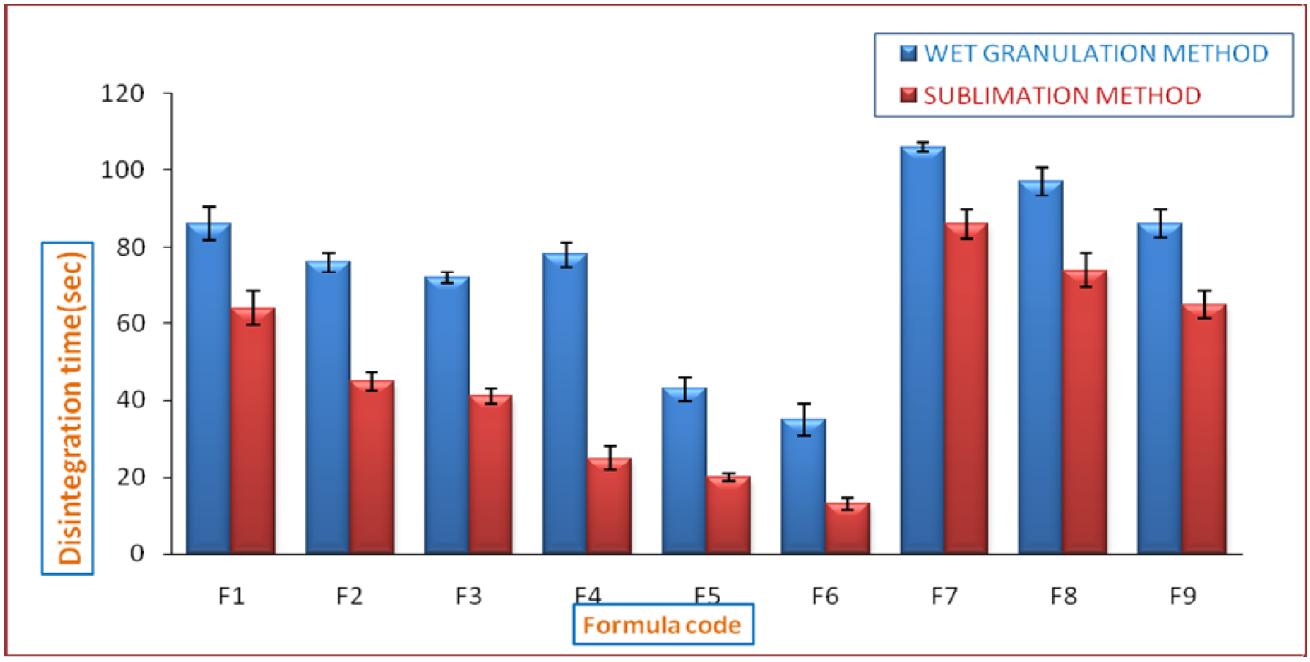

Figure 1. Disintegration time profile of orodispersible tablets

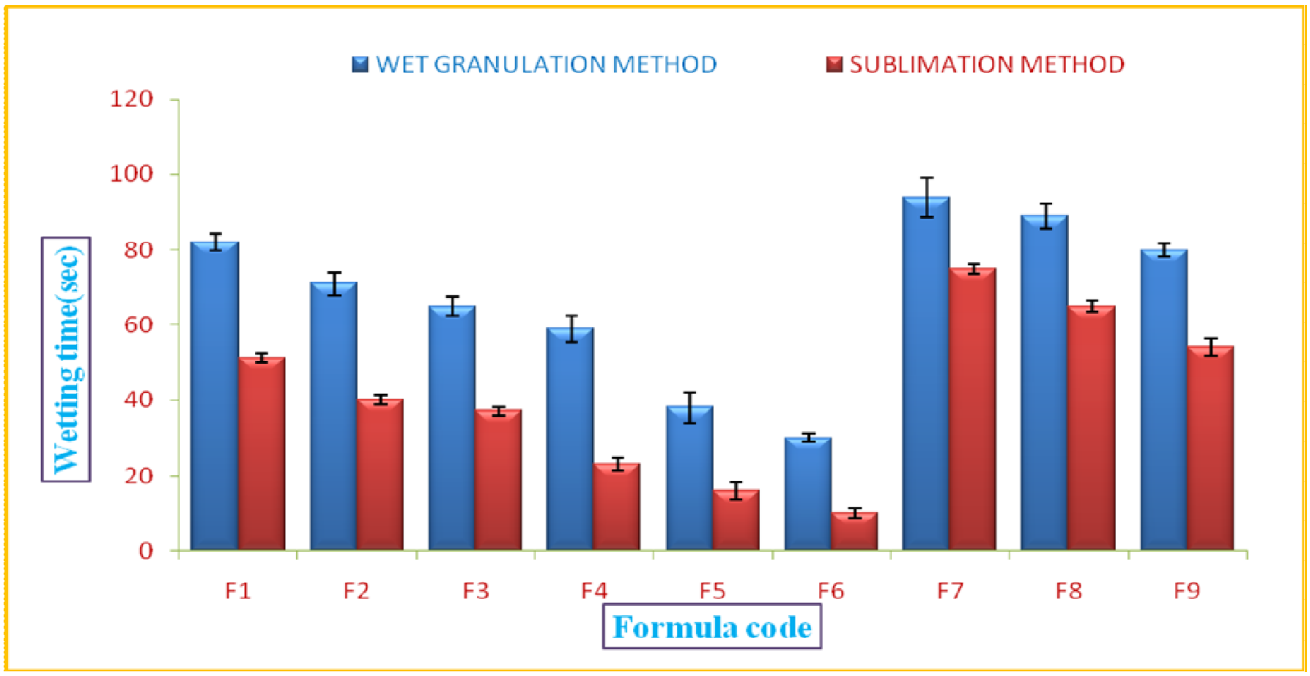

Figure 2. Comparision of wetting time profile of orodispersible tablets

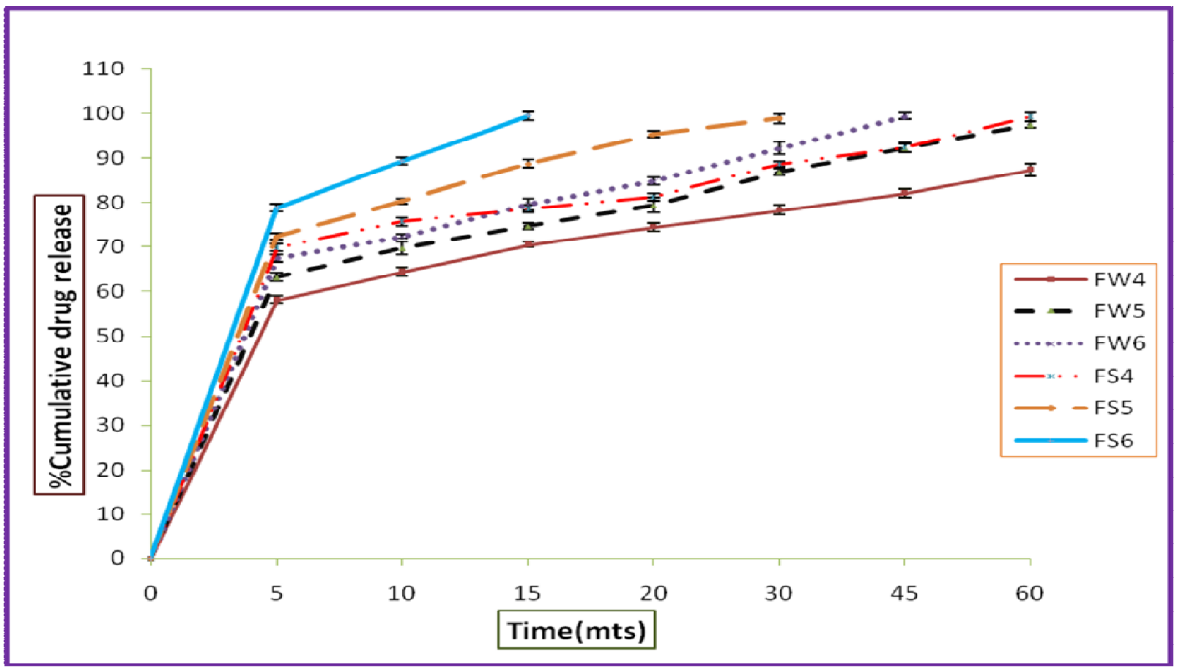

Figure 3. Comparison of cumulative % drug release of orodispersible tablets incorporated with Cross povidone