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Formulation and Characterization of Ziprasidone Floating Pellets

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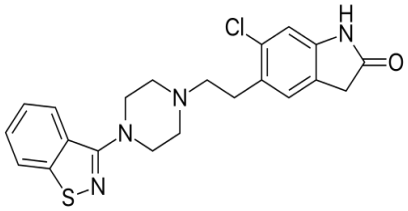
ABSTRACT:
The objective of this study is to design and evaluate Ziprasidone Floating pellets, which prolongs the release rate of the drug while extending the residence time of the drug within the body environment and without causing undeliterious effects to the subject. Ziprasidone and controlled matrix polymer granules were prepared by different granulation techniques in the ratio of 1:1, 1:1.5 and 1:2.Ziprasidone multi unit formulations comprising cellulose polymers were prepared by wet granulation technique, where as the Ziprasidone multi unit formulations comprising lipoidal / fatty polymers were prepared by melt granulation technique. Ziprasidone multi unit formulations with drug and polymer proportion as 1:1, F1 and F2 formulations consisting Cellulose polymers HPMC K4M and HPMC K100 respectively were prepared by wet granulation technique.
Keywords: Ziprasidone, wet granulation, Floating pellets, melt granulation and polymer.

INTRODUCTION

Ziprasidone is a psychotropic agent belonging to the chemical class of benzisoxazole .



$C_{21}H_{21}ClN_4OS$ 5-[2-[4-(1, 2-benzothiazol-3-yl) piperazin-1-yl] ethyl]-6-chloro-1, 3-dihydroindol-2-one.Ziprasidone functions as an antagonist at the dopamine D2 and serotonin 5-HT2A and 5-HT1D receptors, and as an agonist at the 5-HT1A receptor. Ziprasidone also inhibits the synaptic reuptake of serotonin and norepinephrine. The mechanism of action by which Ziprasidone exerts its antischizophrenic effect is unknown but is potentially mediated through a combination of dopamine D2 and serotonin 5-HT2 antagonism. In the absence of food, ziprasidone's oral bioavailability is 60%, and absorption may reach 100% if ziprasidone is taken with a meal containing at least 500 kcal.The mean apparent volume of distribution of Ziprasidone is 1.5 L/kg.It is extensively protein bound with over 99% of the drug bound to plasma proteins, primarily albumin and alpha1-acid glycoprotein. The half life of ziprasidone is 6-7 hours. The present work was carried with an in house experimental design to prepare multi unit granule GFDDS employing successful cellulose

polymers and various efficient lipoidal/fatty polymers with a motto to optimize best polymer among all of them for formulation of hydrodynamically balanced floating drug delivery system of Ziprasidone

FORMULATION DEVELOPMENT

Ziprasidone and controlled matrix polymer granules were prepared by different granulation techniques in the ratio of 1:1, 1:1.5 and 1:2.Ziprasidone multi unit formulations comprising cellulose polymers were prepared by wet granulation technique, where as the Ziprasidone multi unit formulations comprising lipoidal / fatty polymers were prepared by melt granulation technique. Ziprasidone multi unit formulations with drug and polymer proportion as 1:1, F1 and F2 formulations consisting Cellulose polymers HPMC K4M and HPMC K100 respectively were prepared by wet granulation technique.

PREPARATION OF ZIPRASIDONE MULTI UNIT GFDDS BY WET GRANULATION TECHNIQUE

1. Drug and polymer were weighed according to the experimental design, were passed through 40 # sieve separately and blended thoroughly.
2. The blend was granulated with PVP K30 solution which was prepared by dissolving PVP K30 in Iso propyl alcohol.
3. The wet mass was passed through 16# sieve and dried at 65^{o}C for one hour.

Ziprasidone multi unit formulations with drug and polymer proportion as 1:1,and formulations consisting lipoidal / fatty polymers i.e., Compritol 888 and Gelucire 43/01 were prepared by melt granulation technique.

PREPARATION OF ZIPRASIDONE MULTI UNIT GFDDS BY MELT GRANULATION TECHNIQUE

1. Drug and the polymer were weighed according to the experimental design.
2. The lipoidal polymer was taken into a beaker and melted above 5^{o}C of their corresponding melting points.
3. Drug that is priorly passed through 40# sieve was dispersed in the polymer melt by continuous agitation.
4. Drug dispersed melt was allowed to solidify at 4^{o}C.
5. The solidified mass was passed through 16# sieve to attain uniform sized granules.

Table: 1. Compositions of Formulations F1-F12

DRUG : POLYMER PROPORTION - 1: 1, 1:1.5 &1:2

FORMULA	F 1 (mg)	F 2 (mg)	F 3 (mg)	F 4 (mg)	F 5 (mg)	F 6 (mg)	F 7 (mg)	F 8 (mg)	F 9 (mg)	F 10 (mg)	F 11 (mg)	F 12 (mg)
Ziprasidone	80	80	80	80	80	80	80	80	80	80	80	80
HPMC K4M	80	--	--	--	120	--	--	--	160	--	--	--
HPMC K100	--	80	--	--	--	120	--	--	--	160	--	--
Compritol 888 ATO	--	--	80	--	--	--	120	--	--	--	160	--
Gelucire 43/01	--	--	--	80	--	--	--	120	--	--	--	160

Ziprasidone multi unit formulations with drug and polymer proportion as 1:1.5, F5 and F6 formulations and with drug and polymer proportion as 1: 2, F9 and F10 formulations

consisting Cellulose polymers HPMC K4M and HPMC K100 respectively were prepared by wet granulation technique. Ziprasidone multi unit formulations with drug and polymer proportion as 1:1.5, F7 and F8 formulations and with drug and polymer proportion as 1: 2, F 11 and F12 formulations consisting lipoidal / fatty polymers i.e., Compritol 888 ATO, and Gelucire 43/01 were prepared by melt granulation technique.

PREPARATION OF STANDARD SOLUTION FOR STANDARD GRAPH

100mg of Ziprasidone was accurately weighed and taken into a 100ml volumetric flask, to this 1.2 pH HCl was added to dissolve the drug and volume was made up to 100ml with 1.2 pH HCl and mixed, necessary dilutions were made to give concentration of Ziprasidone ranging from 2 to 10 µg/ml solutions.

METHOD FOR STANDARD PLOT OF ZIPRASIDONE

The volumetric solutions were scanned in a UV-Visible spectrophotometer to determine the λ max (318 nm) of the drug. The absorbance of the volumetric solutions was recorded at λ max of the drug and plotted graphically to give the standard graph of Ziprasidone.

STANDARD PLOT OF ZIPRASIDONE

The standard graph of Ziprasidone in 0.1N HCl showed a good linearity with R^2 of 0.9993, in the concentration range of 2-10 µg/ml.The pharmaceutical compositions are designed as multi units, to be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping.Ziprasidone and controlled matrix polymer granules were prepared by different granulation techniques in the ratio of 1:1, 1:1.5 and 1:2. Ziprasidone multi unit formulations with drug and polymer proportion as 1:1, F1 and F2 formulations consisting Cellulose polymers HPMC K4M and HPMC K100 respectively were prepared by wet granulation technique.

Table: 2. Standard Plot Values of Ziprasidone at 318 nm

CONCENTRATION(µg /ml)	ABSORBANCE
0	0
2	0.084
4	0.183
6	0.273
8	0.364
10	0.468

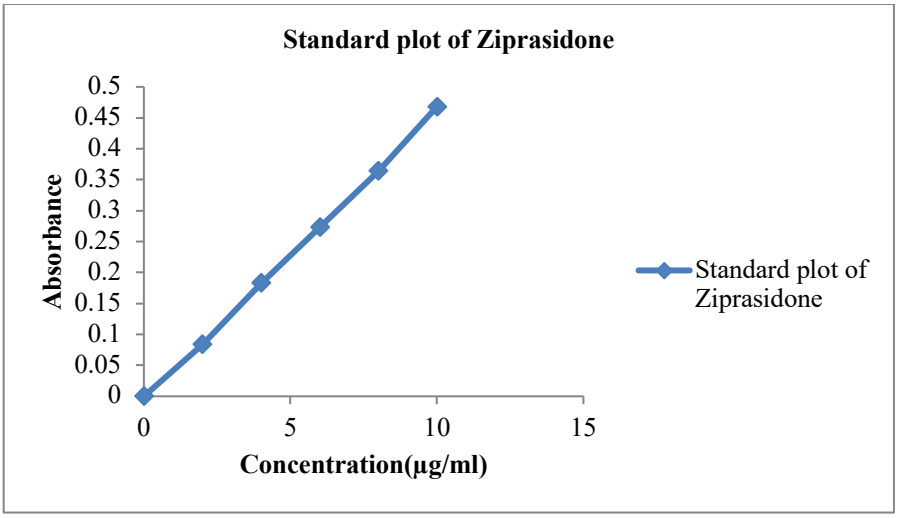


Figure 1: Standard Plot of Ziprasidone at 318 nm

Ziprasidone multi unit formulations with drug and polymer proportion as 1:1, F3 and F4 formulations consisting lipoidal / fatty polymers i.e., Compritol 888 ATO and Gelucire 43/01 were prepared by melt granulation technique.The drug content estimated was found to be within the specified limits i.e., less than ± 5% variation of the stated amount of Ziprasidone. All the multi unit granule GFDDS were evaluated for the physical parameters like Bulk density, Tapped density, Compressibility Index, Hausner ratio and Angle of repose. Granules comprising cellulose polymers has shown good flow properties where as granules comprising lipoidal polymers has shown results inferior to that of cellulose polymers as they are prepared by melt granulation technique, but are passable.

Table: 3. Assay values of the prepared formulations

FORMULATION	DRUG CONTENT (%)
F1	98.23
F2	99.65
F3	99.12
F4	98.44
F5	99.23
F6	98.63
F7	99.65
F8	98.65
F9	98.45
F10	99.64
F11	98.12
F12	99.72

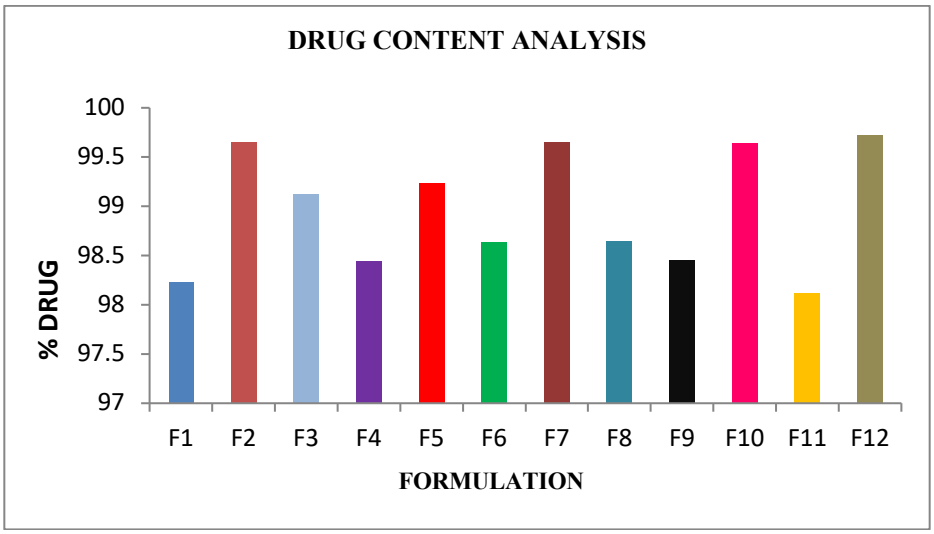


Figure 2: Assay values of the prepared formulations

Table 4: Flow properties of the prepared formulations

FORMULATION	ANGLE OF REPOSE
F1	20.6°
F2	23.5°
F3	31.2°
F4	30.7°
F5	26.8°
F6	33.1°
F7	32.8°
F8	20.9°
F9	24.2°
F10	31.7°
F11	31.2°
F12	30.8°

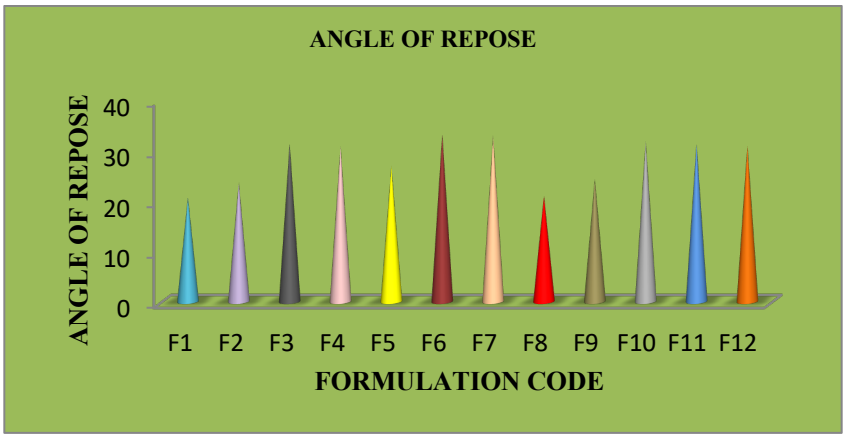


Figure 3: Flow properties of the prepared formulations

The entire prepared multi unit granule GFFDS were subjected to *in vitro* buoyancy studies that are carried out in 0.1 N HCl. All the formulations F1-F12 were tested for floating parameters like Floating lag time and floating duration time

Table 5: *Invitro* Buoyancy Results of Prepared Formulations

Formula	Buoyancy Lag Time (Min)	Duration of Floating (Hrs)
F1	20 min	>12
F2	35 min	>12
F3	---	>12 (10-20%) ↓
F4	---	>12
F5	---	>12
F6	---	>12
F7	---	>12 (10-20%) ↓
F8	25 min	>12
F9	42 min	>12
F10	---	>12
F11	---	2 (60%) ↓
F12	---	>19

Formulations prepared with cellulose polymers in different drug to polymer proportions (F1, F2, F5, F6, F9, F10) had shown buoyancy lag time which might be the time taken for hydrogel formation, where as all the other formulations prepared with lipoidal polymers in different drug to polymer proportions had floated from zero time. But in case of multi unit formulations prepared with Compritol 888 ATO 10-20% and 60% of granules respectively had shrinked to the bottom after 2 hours. Other multi unit GFDDS prepared with Gelucire 43/01 had shown excellent buoyancy characteristics beyond 12 hours of study.

Table: 6. Cumulative % release of Formulations F1-F4

Time (Hrs)	F1	F2	F3	F4
0	0	0	0	0
0.5	10.52±1.50	13.37±1.20	26.62±1.75	4.17±1.02
1	15.31±0.75	28.15±0.89	33.74±1.64	8.11±1.45
1.5	22.34±0.68	41.22±0.86	42.17±0.84	13.13±0.12
2	38.73±1.22	59.05±0.64	51.64±1.26	17.43±0.65
3	57.22±1.44	71.29±1.23	63.21±0.92	26.28±1.45
4	65.29±0.69	82.38±1.44	71.4±0.35	35.34±1.79
5	86.03±0.98	96.82±1.28	79.32±0.46	47.66±1.34
6	95.07±1.10		86.47±1.25	62.6±0.15
8			98.61±0.24	73.47±0.49
10				87.32±0.97
12				98.96±0.84

MEAN±S.D n=3

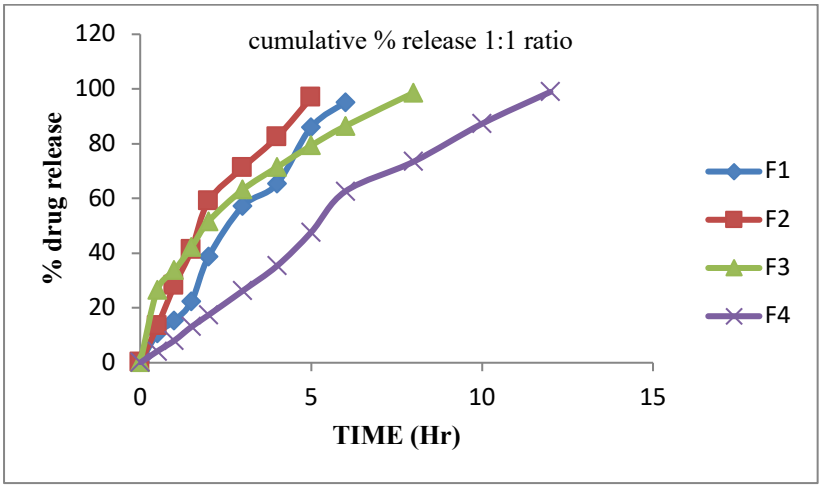


Figure 4: Comparative Dissolution Profiles of Formulations F1-F4

Table 7: Cumulative % release of Formulations F5-F8

Time (Hrs)	F5	F6	F7	F8
0	0	0	0	0
0.5	9.74±0.94	11.43±1.76	6.23±1.28	2.15±1.48
1	13.81±1.48	23.31±1.34	10.56±1.46	4.47±1.46
1.5	20.31±1.78	37.4±0.18	16.19±1.28	9.84±1.79
2	34.74±0.18	51.62±0.49	26.23±1.26	12.29±0.48
3	43.29±0.64	64.17±1.26	39.26±1.34	18.21±0.94
4	55.57±1.97	72.39±1.28	48.63±0.24	24.93±0.87
5	63.36±1.46	81.2±0.48	56.66±0.97	33.36±0.89
6	71.28±1.87	95.51±1.49	64.63±0.67	43.49±1.87
8	83.11±0.48		77.34±1.48	49.21±1.26
10	93.27±1.34		85.76±0.67	55.59±1.48
12			92.28±0.42	62.93±0.54

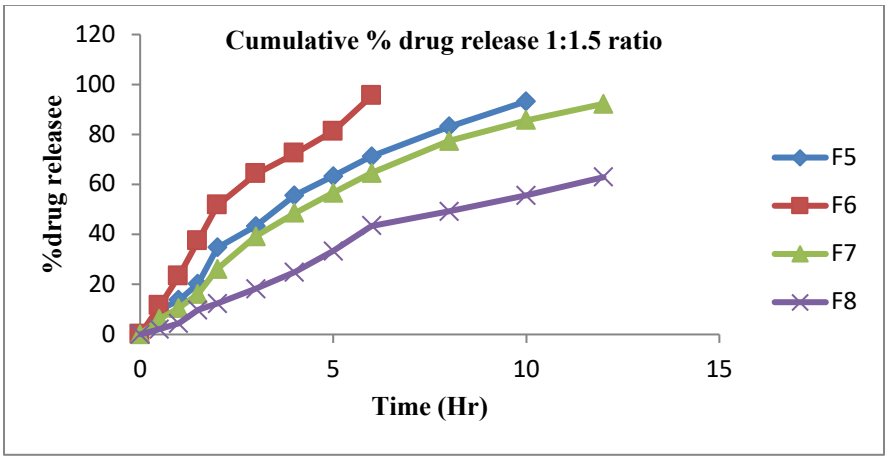


Figure 5: Comparative Dissolution Profiles of Formulations F5-F8

Table 8: Cumulative % release of Formulations F9-F12

Time (Hrs)	F9	F10	F11	F12
0	0	0	0	0
0.5	5.63±1.72	10.41±1.25	4.24±1.32	3.23±1.26
1	9.94±2.34	19.62±1.75	8.82±1.56	6.48±0.64
1.5	14.31±1.69	31.53±2.76	13.87±0.24	8.59±2.22
2	21.16±0.84	43.6±0.48	19.39±0.65	11.96±0.84
3	30.42±0.97	52.77±0.29	23.93±1.24	17.59±0.91
4	39.63±1.12	64.31±1.64	34.42±2.01	23.54±1.12
5	45.51±0.78	76.56±1.35	47.31±1.34	29.89±1.35
6	56.05±0.11	85.19±0.92	59.2±1.56	36.38±0.98
8	63.37±0.32	98.23±1.21	65.12±0.95	40.54±1.23
10	74.4±1.44		73.37±0.32	44.73±0.86
12	83.37±0.24		87.11±1.47	49.77±1.44

MEAN±S.D n=3

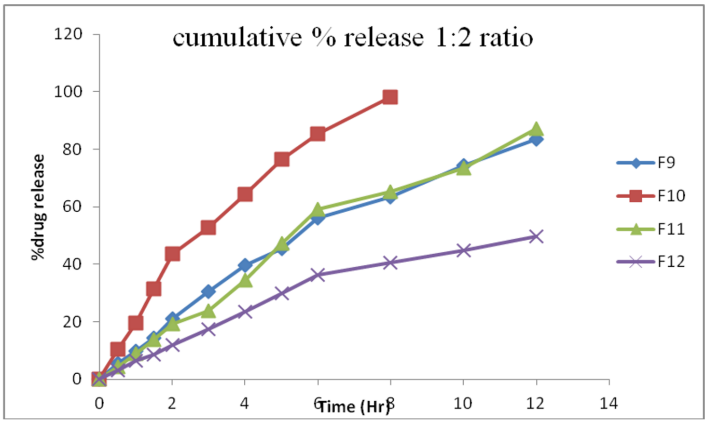


Figure 6: Comparative Dissolution Profiles of Formulations F9-F12

The *in vitro* drug release studies of the entire prepared multi unit GFDDS were studied separately according to their proportions (1:1, 1:1.5 and 1:2) using 0.1 N HCl as medium in USP XXIV paddle type dissolution apparatus.

Table 9: Cumulative % release of Single Unit Formulation

Time (Hrs)	SINGLE UNIT
0	0
0.5	2.43±1.28
1	5.58±0.91
1.5	9.07±2.06
2	16±0.78
3	27.51±1.74
4	36.12±0.86
5	43.57±0.71
6	57.66±0.68
8	64.24±1.22
10	70.58±0.98
12	81.09±0.68

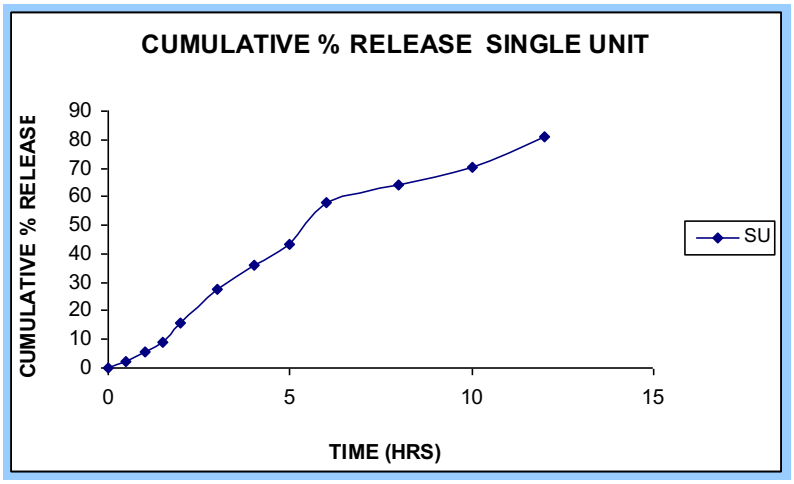


Figure 7: Dissolution Profile of Single Unit Formulation

The dissolution characteristics of optimized multi unit formulation F7 is compared with that of the pure drug and Marketed formulation (Zeldox). Pure drug had shown its high hydrophilic characteristics by releasing 93% of drug in 0.5 hours itself, where as Ziprasidone marketed formulation had shown drug release of more than 97% in 1 hour.

Table 10: Cumulative % release of Formulations F7, Zeldox, Pure Drug

Time (Hrs)	F4	ZELDOX	PURE DRUG
0	0	0	0
0.5	4.17±1.02	61.53±2.06	93.37±2.02
1	8.11±1.45	97.81±1.49	
1.5	13.13±0.12		
2	17.43±0.65		
3	26.28±1.45		
4	35.34±1.79		
5	47.66±1.34		
6	62.6±0.15		
8	73.47±0.49		
10	87.32±0.97		
12	98.96±0.84		

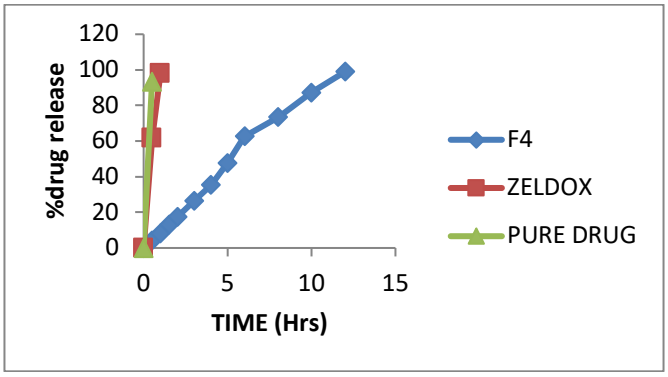


Figure 8: Comparative Dissolution Profiles of Formulations F4, Single Unit Formulation, Zeldox, Pure Drug

DRUG RELEASE KINETICS

In order to establish the mechanism of drug release, the experimental data was fitted to five popular exponential equations.

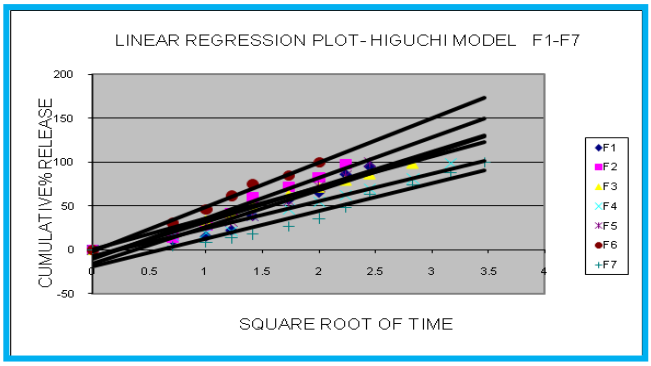


Figure 9: Linear Regression Plots for the Dissolution profiles of Ziprasidone Multi Unit GFDDS (Drug: Polymer - 1:1) Higuchi Plot

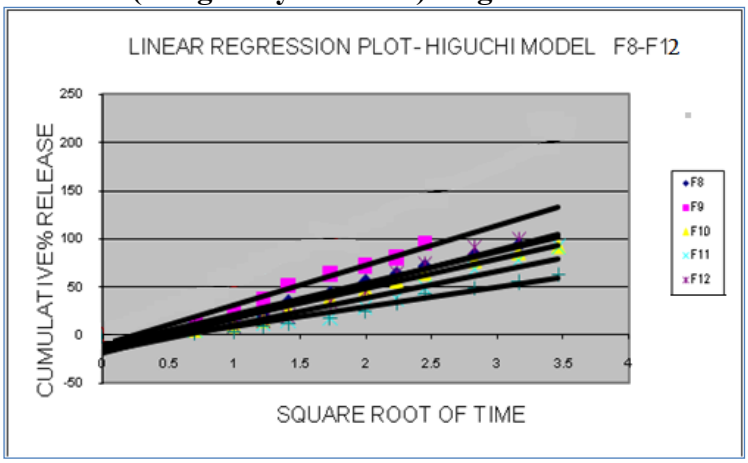


Figure 10: Linear Regression Plots for the Dissolution profiles of Ziprasidone Multi Unit GFDDS (Drug: Polymer - 1:1.5) Higuchi Plot

Table: 11. Correlation Coefficient (r) values and Release kinetics of Ziprasidone Multi Unit GFDDS (Drug to polymer proportion- 1:1) with Single unit, Marketed sample "Zeldox" and Pure Drug

Formulation	Zero Order		First Order		Diffusion	Erosion	Pappas Equation		T_{50} (Hours)	T_{80} (Hours)
	K_O	R	K_1	R	R	R	R	N		
F1	37.58	0.973	0.122	0.028	0.923	0.035	0.67	1.73	2.5	4.5
F2	44.01	0.956	0.158	0.030	0.962	0.025	0.507	1.75	1.8	3.8
F3	25.42	0.905	0.207	0.123	0.988	0.090	0.47	1.26	1.9	5.2
F4	21.07	0.956	0.145	0.098	0.975	0.086	0.61	1.25	3.5	8
F5	35.16	0.981	0.377	0.907	0.953	0.077	0.54	1.54	2.5	4.5
F6	52.87	0.906	0.384	0.087	0.972	0.028	0.40	1.95	1.2	2.5
F7	19.96	0.987	0.181	1.851	0.995	0.161	0.81	1.36	4.5	9
Single Unit	16.60	0.962	0.089	0.99	0.946	0.003	0.975	1.992	5.5	11.8
Pure Drug	428.9	1	5.435	1	1	1	0.996	1.187	0.3	0.75
ZELDOX	225.25	0.971	0.221	0.92	0.992	0.49	0.993	1.196	0.1	0.4

Table: 12. Correlation Coefficient (r) values and Release kinetics of Ziprasidone Multi Unit GFDDS (Drug to polymer proportion- 1:1.5) with Single unit, Marketed sample "Zeldox" and Pure Drug

Formulation	Zero Order		First Order		Diffusion	Erosion	Pappas Equation		T_{50} (Hours)	T_{80} (Hours)
	K_O	R	K_1	R	R	R	R	N		
F8	21.80	0.952	21.80	0.044	0.971	0.063	0.66	1.32	3.5	7
F9	35.32	0.951	35.32	0.023	0.968	0.028	0.54	1.55	1.8	4.5
F10	18.47	0.947	18.47	0.065	0.980	0.092	0.72	1.27	4.5	9
F11	17.91	0.991	0.059	0.031	0.910	0.056	0.80	1.36	7	11
F12	24.57	0.978	0.218	0.018	0.928	0.150	0.77	1.46	4.5	7
Single Unit	16.60	0.962	0.089	0.99	0.946	0.003	0.975	1.992	5.5	11.8
Pure Drug	428.9	1	5.435	1	1	1	0.996	1.187	0.3	0.75
ZELDOX	225.25	0.971	0.221	0.92	0.992	0.49	0.993	1.196	0.1	0.4

K_O is the zero order release rate constant, R= correlation coefficient, K_1 is the first order release rate constant.

Theoretical release profile of a drug is constructed to check whether the formulations are releasing the drug similar to the predicted profile. Drug release from the optimized formulation F4 is compared with that of the theoretical release profile.

Table 13: Comparative Data of Theoretical Drug Release and F4 Formulation

TIME (HRS)	THEORITICAL RELEASE	CUMULATIVE % RELESE OF F7
0	0	0
2	28.3	17.43
4	42.24	35.34
6	56.1	62.6
8	69.96	73.47
10	79.86	87.32
12	97.68	98.96

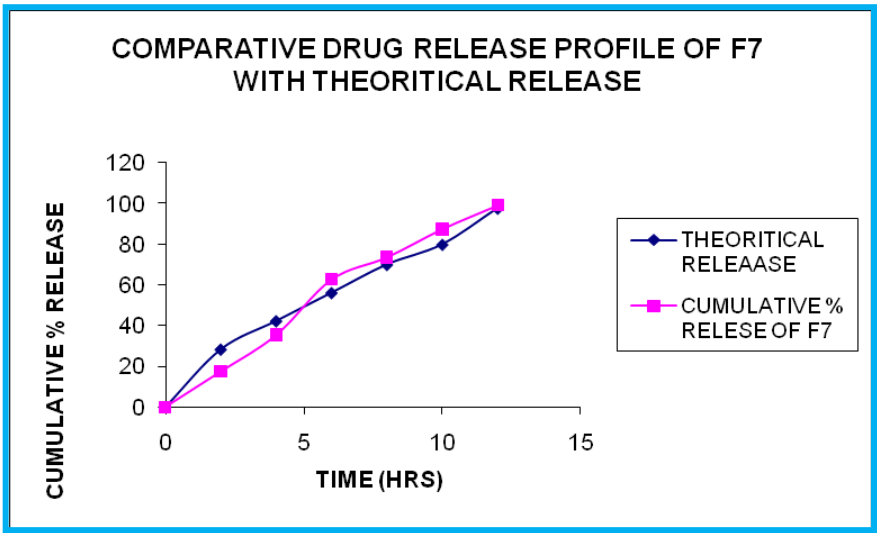


Figure 11: Comparative Drug Release Profile of Formulation with Theoretical Release

By comparing the dissolution profile it was found that the drug release from the optimized formulation is almost similar to that of the theoretical drug release. In order to establish the mechanism of drug release, the experimental data was fitted to five popular exponential equations.The drug release of Ziprasidone prepared from cellulose polymers (by wet granulation) and from the Lipoidal / fatty polymers (by melt granulation) followed zero order kinetics which was clearly indicated by higher "r" values of Zero order release when compared o those of first order release model.The relative contributions of drug diffusion and matrix erosion to drug release were further confirmed by subjecting the dissolution data to Higuchi model and Erosion model. It was found that all the formulations followed diffusion mechanism as indicated by their higher "r" values

Summary and Conclusion

Ziprasidone multi unit granule GFDDS with controlled matrix cellulose and lipoidal polymers were prepared by different granulation techniques in the ratio of 1:1, 1:1.5 and 1:2.All the multi unit granule formulations (F1 to F12) prepared were evaluated for drug content and all the formulations had shown good results within the official limits.GFDDS prepared with Gelucire 43/01 had shown excellent buoyancy characteristics beyond 12 hours of study.The *in*

vitro drug release studies of the entire prepared multi unit GFDDS were studied separately according to their proportions (1:1, 1:1.5 and 1:2) using 0.1 N HCl as medium in USP XXIV paddle type dissolution apparatus.The optimized formulation F4 was evaluated for its floating ability and *in vitro* drug release studies against single unit GFDDS prepared employing same polymer i.e., Gelucire 43/01with drug to polymer ratio of 1:3. By comparing the buoyant characteristics and release characteristics among F4 and single unit, single unit GFDDS had shown excellent floating ability for more than 12 hours, also the drug release was found to be 81% for 12 hours, by an unknown mechanism of drug release, very promising in vitro results were observed with multi unit floating formulations of Ziprasidone.

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