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Design and Evaluation of Extended release tablet of Venlafaxine Hydrochloride using Compression coating method

K. V. Krishna, K. Satyavathi, M. Venu

Department of Pharmaceutical Technology, Koringa College of Pharmacy (Andhra Pradesh)

***Abstract*-** Venlafaxine Hcl is an anti-depressant drug which is used in depression. The aim of present investigation was to prepare an ER tablet of Venlafaxine Hcl with similar dissolution profile matching to Effexor ER. An immediate release core tablet of 100mg was prepared and it was compression coated using HPMC matrix system. HPMC of three viscosity grades i.e., K4M, K15M, K100M and different concentrations of 15% polymer, 25% polymer, 35% polymer & 45% polymer were taken. With the above polymers by using wet granulation and direct compression process 24 formulations were prepared. The data obtained from in vitro drug release was used to determine the similarity factor between marketed and optimized product. Out of all F7 formulation (K15M 35% polymer) is optimized and is matching with the marketed product.

***Index Terms*-** Venlafaxine Hcl, Extended release tablet, Compression coating method

I. INTRODUCTION

Venlafaxine HCl is a structurally novel antidepressant drug, and is usually categorized as serotonin-norepinephrine reuptake inhibitor (SNRI), but it is referred as serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI). Its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α-1 adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity. Venlafaxine is well absorbed and extensively metabolized in the liver. The half-life of Venlafaxine was 5 to 7 hours so must be given two or three times to maintain adequate plasma concentration. The present work was carried out to develop extended release venlafaxine tablet to be given once daily. The main objective of the present work was to develop a swelling matrix type drug delivery platform system for Venlafaxine HCl which will have dissolution profile similar to Effexor XR capsules. To develop a platform technology for Venlafaxine sustained release tablets using compression coating as technique for controlling drug release. Drug loaded pellets of Venlafaxine HCl were enrobed in a HPMC matrix by the compression coating technique. The cup: cap technology was used for the compression coating due to its novelty, easy of fabrication and excellent reproducibility.

Design and Development:

Venlafaxine IR Formulation:

The experimental work was performed in the following sequence:

1. Dissolution profile of the innovator product (Effexor XR) was performed to determine the target.
2. Drug loading of Venlafaxine HCl on to sugar pellets as per standardized method.
3. Preparation of coating material formulations using different viscosity grade polymers each at 15%, 25%, 35% and 45% concentration for compression coating by the wet granulation method. Characterization of the granules.
4. Compression coating of drug loaded pellets (2) with coating formulations(3)
5. Preparation of coating material formulations using different viscosity grade polymers each at 15%, 25%, 35% and 45% concentration for compression coating by the direct compression method.
6. Compression coating of drug loaded pellets (2) with coating formulations (5).
7. Dissolution profiles for compression coated tablets (4) and (6) in 0.1N HCl as per the USP method.

II. DISSOLUTION PROFILE OF EFFEXOR XR CAPSULES

The dissolution profile of Effexor XR 37.5 mg capsules was carried out on 6 units as per the following conditions:

Apparatus	: USP Type II
Media	: 900 ml 0.1N HCl
Temperature	: 37.5±0.2°C
r.p.m	: 50 rpm
Sampling time points (hours)	: 1, 2, 4, 8, 12 and 20
Analytical Method	:UV spectroscopy at 274 nm.

III. LOADING OF DRUG VENLAFAXINE HCL ON TO NON-PERIL SUGAR BEADS

The Wooster column fitted to the Niro STREA fluidized bed coating system was used to load Venlafaxine HCl on to sugar beads. The formula and process is as given below:

Table: 1 Unit Composition formula for Venlafaxine HCl Loading

S.No.	Ingredient	CF1	CF2	CF3	CF4
1	Sugar Spheres (20/25)	43.571	43.571	43.571	43.571
2	Venlafaxine HCl	42.429	42.429	42.429	42.429
3	HPMC 6 cps	2.000	3.000	4.000	5.000
4	Talc	12.500	11.500	10.500	9.500
5	Purified Water	q.s	q.s	q.s	q.s
	Total Drug Loaded Pellets	**100.500**	**100.500**	**100.500**	**100.500**

Procedure:

1) Venlafaxine HCl was added to 60% of the total water in a beaker and stirred till completely dissolved
2) To 40% of the balance water, HPMC 6 cps was added slowly with constant stirring at medium speed taking care to avoid foaming and lump formation. After the powder has been completely added, the stirring was continued at slow speed for 30 minutes to completely disperse the HPMC
3) Solution (2) was added to (1) under continuous stirring
4) Talc was added to solution (3) and stirring was continued for 60 minutes.
5) The dispersion was filtered thru # 200 bolting cloth to remove any lumps or extraneous matter.
6) The 20/25 fraction of sugar spheres were loaded into the STREA and preheated to 37 °C.
7) The drug dispersion (5) was sprayed at an optimum rate of 1 to 3 ml/min through 1.0 mm spray nozzle, 50°C inlet temperature and 40°C exhaust temperature. The atomizing air pressure was adjusted to 2.5 psi.
8) At the end of the spraying, the pellets were allowed to dry in the STREA at 55° C inlet temperature for 30 minutes.
9) The drug loaded pellets were analyzed for drug content and dissolution profile.

IV. Formulation of Coating Material by Wet Granulation Process

A series of granules (Table 2) with 4 levels of each of HPMC K4M, K15M and K100M were prepared by the wet granulation technique.

Table: 2 Unit Composition Formula for Coating Layer (Wet Granulation Process)

Ingredients		**15% Polymer**			**25% Polymer**			**35% Polymer**			**45% Polymer**		
		F1 (mg)	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**	**F10 (mg)**	**F11 (mg)**	**F12 (mg)**
HPMC	**K4M**	**120**			**200**			**280**			**360**		
HPMC	**K15M**		**120**			**200**			**280**			**360**	
HPMC	**K100M**			**120**			**200**			**280**			**360**

PVP	**K30**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Lactose	**Mono-hydrate**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
Avicel	**PH101**	**348**	**348**	**348**	**268**	**268**	**268**	**188**	**188**	**188**	**108**	**108**	**108**
Mag.	**Stearate**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Aerosil	**200 P**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Total		**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**	**800**

Wet Granulation Process:

- **Sifting:**
  HPMC, Lactose and Avicel were sifted through #20mesh and Magnesium stearate was shifted #40 mesh sieve and are collected separately.
- **Dry mixing:**

Mixing of HPMC, Lactose and Avicel 101 was done in RMG (10L Capacity) for 10 min with impeller slow speed and chopper off.

- **Binder preparation:**

Povidone (PVP K30) dissolved in purified water to form binder solution.(25%w/v solution)

- **Granulation:**
  Binder solution added slowly for 90 sec with chopper off. Then kneading carried out for 120 sec with chopper slow and impeller fast.

Table: 3 Granulation Sequence

Condition	Time	Impeller Speed	Chopper
Dry Mixing	1200 sec	100 rpm	0
Binder Addition	90 sec	150 rpm	0
Mixing time	60 sec	150 rpm	0
Mixing time	60 sec	150 rpm	0
Kneading Time	120 sec	150 rpm	1000 rpm
Removal	60 sec	100 rpm	0

- **Drying:**
  1.Wet mass was dried in fluid bed dryer at 60°C until the loss on drying was not more than 1.2 % w/ w. (Determined by Moisture analyzer at 85°C)
  2.Pooled sample from different locations of Fluid Bed Dryer bowl were taken and Loss on Drying (LOD) was studied at 60°C on Moisture Balance the LOD after drying was - below 0.95% .
- **Milling & sifting:**

Dried granules were sifted through # 20 and the retentions were milled through 1.0 mm screen, medium speed with knives forward direction in comminuting mill. The milled material was sifted through # 20mesh. Process continued till all the dried granules pass through # 20 mesh

- **Blending:**

The dried granules were loaded in an Octagonal Blender, Magnesium stearate and Aerosil were added and blended for 5 minutes at 8 rpm.

The dried granules were characterized by following methods:

1. Angle of repose
2. Bulk density
3. Tapped density
4. Compressibility index
5. Hausner's ratio

Formulation of Coating material by Direct Compression Technique

A series of granules (Table: 4) with 4 levels of each of HPMC K4M, K15M and K100M were prepared by the direct compression technique.

Table: 4 Unit Composition Formula for Coating Layer (Direct Compression Technique)

Ingredients		15% Polymer			25% Polymer			35% Polymer			45% Polymer		
		F13 (mg)	F14 (mg)	F15 (mg)	F16 (mg)	F17 (mg)	F18 (mg)	F19 (mg)	F20 (mg)	F21 (mg)	F22 (mg)	F23 (mg)	F24 (mg)
HPMC	K4M	120			200			280			360		
HPMC	K15M		120			200			280			360	
HPMC	K100M			120			200			280			360
PVP	K30	20	20	20	20	20	20	20	20	20	20	20	20
Lactose	Anhydrous	300	300	300	300	300	300	300	300	300	300	300	300
Avicel	PH102	348	348	348	268	268	268	188	188	188	108	108	108
Mag.	Stearate	8	8	8	8	8	8	8	8	8	8	8	8
Aerosil	200 P	4	4	4	4	4	4	4	4	4	4	4	4
Total		800	800	800	800	800	800	800	800	800	800	800	800

Blend Preparation for the Direct Compression Technique:

- **Sifting:**
  HPMC, Lactose and Avicel were sifted through #20mesh and Magnesium stearate was shifted #40 mesh sieve and are collected separately.
- **Blending Sequence:**
  (1) HPMC and PVP are loaded in the blender and mixed for 5 minutes.
  (2) The blend is unloaded and co sifted with Lactose Anhydrous.
  (3) The co sifted material is then loaded into the blender and blended for 5 minutes.
  (4) The blend is unloaded and co sifted with Avicel PH 102.
  (5) The co sifted mixture is again loaded into the blender and blended for 15 minutes.
  (6) To this, Aerosil and Magnesium stearate are added and blended for 5 minutes

V. Compression Coating (for both processes)

Compression coating was carried out using 12.5 mm circular die punch set using the following sequence of compression

(1) 400 mg of the coating formulation was placed in the die cavity

(2) This was compressed to give a soft compact

(3) In this compact a 6 mm cavity was created.

(4) In this cavity, 100 mg of Venlafaxin HCl pellets were carefully placed (equivalent to 37.5 mg of Venlafaxine HCl)

(5) Then 400 mg of the coating material was overlaid and the final compression was carried out.

(6) The compressed tablets were evaluated for Weight, thickness, hardness, friability, Assay and dissolution profile in 0.1N HCl.

Tooling:

12.5mm hollow punch with a 6.5 mm bit

Evaluation of tablets:

Thickness:

Twenty tablets from representative sample are randomly taken and individual thickness of tablet was measured by using a

digital vernier calipers. Average thickness and standard deviation values are calculated.

Hardness

Tablet hardness was measured by using the Monsanto hardness tester. From each batch six tablets were measured for hardness and the average of six values was noted along with the standard deviations.

Friability Test:

From each batch, 10 tablets were accurately weighed and then placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as percentage weight loss.

Note: No tablet should stick to the walls of apparatus. If so, brush the walls with talcum powder. There should be no capping also.

% Friability was calculated as follows

$$\% \text{ Friability} = (W1 - W2)/W1 \times 100$$

where W1 = Initial weight of the 20 tablets.

W2 = Final weight of the 20 tablets after testing.

Friability values below 1 % are generally acceptable.

Weight Variation Test:

To study the weight variation, individual weights (WI) of 20 tablets from each of formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (WA - WI)/WA \times 100$$

As the total tablet weight was 800 mg, according to USP 1996, out of twenty tablets ±5%, variation can be allowed for not more than two tablets.

VI. In vitro Drug Release Studies

The in vitro drug release study was performed for the single- & multiple-unit tablets using USP Type II dissolution apparatus under the following conditions.

Dissolution test parameters

Medium	:	900ml of 01.N HCl
Rotation speed	:	50 rpm
Temperature	:	37±0.5ºC
Sampling Volume	:	5ml

At predetermined time intervals samples (5 ml) were collected and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 271 nm.

Release kinetics:

To analyze the *in vitro* release data, various kinetic models were used to describe the release kinetics. The drug release profile obtained in dissolution test was plotted in different models.

1. Zero order rate kinetics
2. First order rate kinetics
3. Higuchi square root kinetics
4. Korsmeyer-peppas model
5. Hixson Crowell plot

Results and Discussions:

The dissolution profile for the Effexor XR 37.5 mg capsules is recorded in Table 5 and shown in Fig 1

Based on this profile the target product profile is defined as shown in Table: 5

Table: 5 Dissolution profile for Effexor XR

S.No	Time (hours)	% Drug release
1	0	0
2	1	8.3
3	2	11.5
4	4	23.35
5	8	49.4
6	12	86.85
7	20	99.15

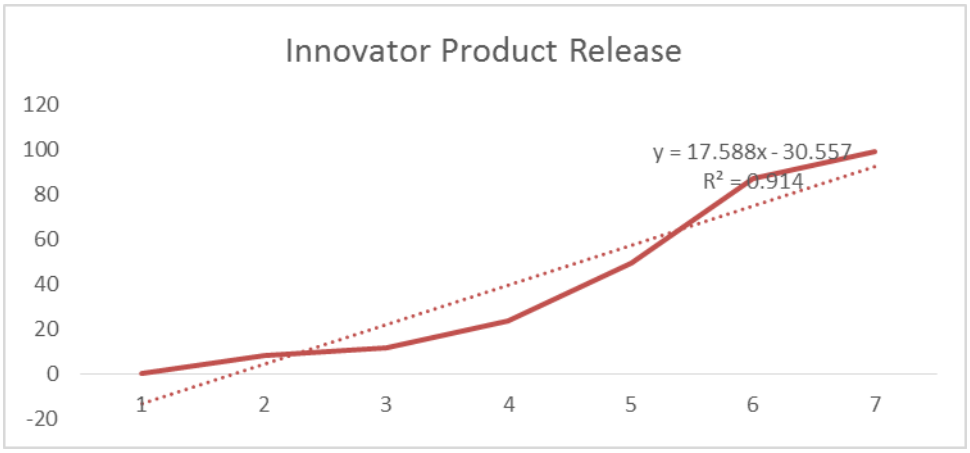

Fig: 1 Dissolution profile of Effexor ER

Assay and Dissolution profile for Drug Loaded Pellets of Venlafaxine HCl:

The assay for the drug loaded pellets was conducted by taking 100 mg of pellets (equivalent to 37.5 mg of Venlafaxin HCl) in 100 ml volumetric flask. 0.1N HCl was added and sonicated for 30 minutes. The volume was made up to 100 ml. The sample was filtered and suitably diluted. The absorbance was measured at 274 nm and % drug content was calculated. This procedure was carried out in triplicate. The mean % drug content was 99.7%

Table: 6 Assay for Venlafacine Hcl

S.No	Time (minutes)	Mean % Drug dissolved
0	0	0
1	10	65
2	15	85
3	30	93
4	45	98
5	60	99.7

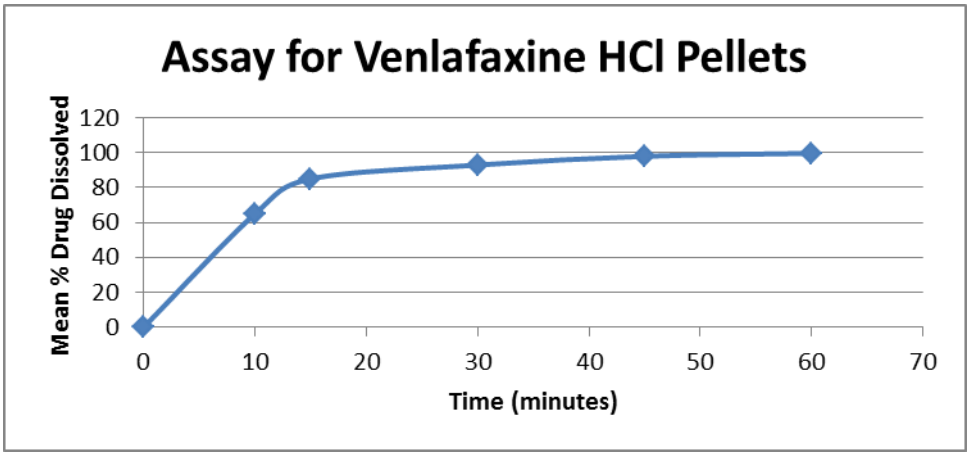

Fig: 2 Assay for Venlafaxine Hcl pellets

The dissolution profile for pellets was carried out in 0.1N Hcl by directly putting 100 mg pellets in each of the dissolution vessel and sampling at 5, 10, 15, 30, 45 and 60 minutes time points. The mean % drug dissolved was calculated and recorded in Table 7:

Table: 7 Dissolution profile of Venlafaxine Hcl pellets

	Mean % Drug Released				
Time (mins)	CF1	CF2	CF3	CF4	TPP
0	0	0	0	0	0
5	4.77	24.28	34.78	40.05	20-30%
10	11.46	58.17	58.75	62.23	55-65%
15	20.66	74.13	82.72	84.15	70-80%
30	43.78	87.82	96.69	99.19	85-95%
45	57.02	94.92	-	-	90-100%
60	63.79	100.00	-	-	-

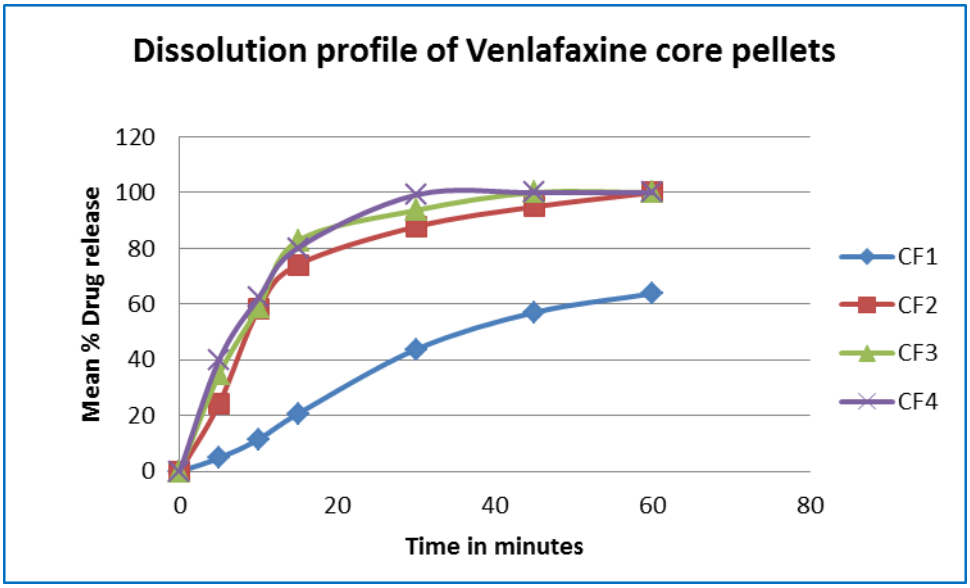

Fig: 3 Dissolution profiles of Venlafaxine core pellets at 274nm

From the dissolution profiles, CF2 follows the TPP and hence the CF2 formulation is finalized and is used further in all the following formulations for preparation of core tablets.

Formulations Prepared by Wet Granulation Technique

Table: 8 Granules characteristics for Coating Material granules

FORMULATION CODE:	BULK BENSITY (gm/ml)	TAPPED DENSITY(gm/ml)	COMPRESIBILITY (%)	HAUSNER RATIO	ANGLE OF REPOSE
F1	0.555	0.617	10.0	1.11	28
F2	0.5	0.625	20.0	1.25	39
F3	0.531	0.632	15.9	1.19	35
F4	0.555	0.632	12.2	1.13	33
F5	0.588	0.714	17.6	1.21	37
F6	0.534	0.632	15.5	1.18	34
F7	0.526	0.606	13.1	1.15	32
F8	0.5	0.613	18.5	1.22	38
F9	0.568	0.666	14.7	1.17	35
F10	0.561	0.675	16.8	1.20	36
F11	0.512	0.595	13.8	1.16	34
F12	0.502	0.519	15.0	1.03	36

Table: 9 The physical properties of tablets are recorded

FORMULATION CODE	Average weight range (mg)	HARDNESS†(Kg/cm^2)	THICKNESS† (mm)	FRIABILITY† (%) w/w	ASSAY*(%)
F1	922.1±2.13	6.3±0.36	6.53±0.06	0.85	99.54
F2	920.6±4.13	5.1±0.58	6.46±0.04	0.83	99.84
F3	919.5±3.13	4.5±0.63	6.54±0.07	0.99	97.44
F4	920.9±5.83	6.1±0.12	6.80±0.09	0.76	99.34
F5	924.8±6.84	5.8±0.22	6.11±0.06	1.38	97.84
F6	917.7±3.46	6.2±0.54	6.39±0.06	0.84	99.44
F7	918.3±6.22	6.6±0.83	6.86±0.05	0.88	98.24
F8	916.9±5.88	5.2±0.28	6.45±0.03	0.92	97.23
F9	922.2±3.44	6.8±0.62	6.29±0.09	0.99	97.55
F10	919.6±3.99	4.3±0.84	6.73±0.07	1.25	98.67
F11	917.8±4.44	6.6±0.32	6.59±0.01	0.99	98.36
F12	923.2±3.67	5.9±0.21	6.86±0.09	1.49	99.23

*All values are expressed as M ±SE, n=20, † All values are expressed as M±SE, n=10.
The tablets prepared by wet granulation technique showed hardness in the range of only 4 to 6 kg and friability was above 0.8% w/w. All the batches passed the test for assay.

Table: 10 Dissolution Profile for Venlafaxine HCl ER tablets prepared by Wet Granulation Method

		k4M %				k15M %				k100 M %			
Time	Effexor XR	15%	25%	35%	45%	15%	25%	35%	45%	15%	25%	35%	45%
	TPP	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	8.3	38.56	28.56	25.78	20.54	23.2	13.2	9.7	6.5	25.67	14.97	2.94	0
2	11.5	76.89	56.89	47.57	36.4	37.89	27.89	15.68	9.7	43.5	20.96	4.44	3.8
4	23.35	95.8	89.8	80.98	49.8	60.98	50.98	25.47	17.68	65.45	32.89	17.2	7.26
8	49.4	98.1	91.1	97.46	81.57	82.38	80.99	54.98	45.24	78.27	44.56	34.5	18.57
12	86.85	99.57	95.57	98.89	90.57	93.86	88.86	92.77	80.57	82.19	70.57	67.8	35.68

20	99.15	100	100	99.54	98.54	98.04	95.54	98.97	87.67	83.46	78.89	70.89	55.79

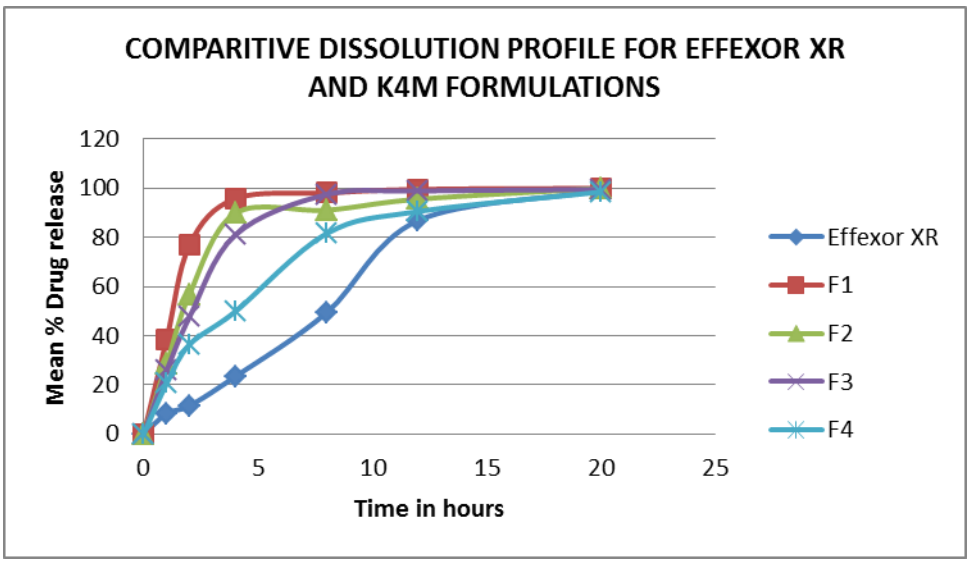

Fig: 4 Comparative Dissolution Profile of Effexor and K4M wet granulation formulations

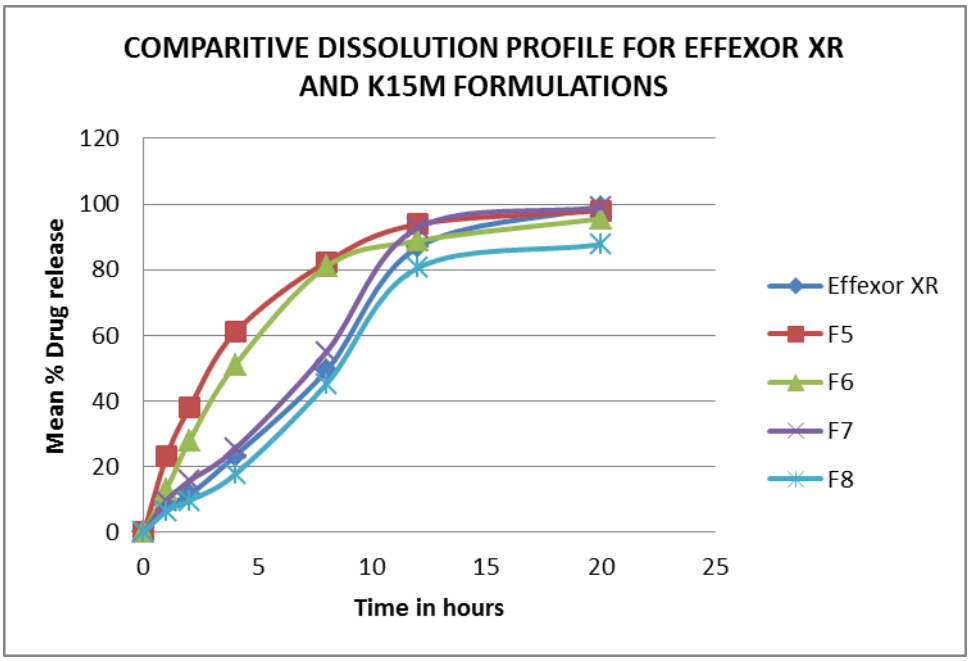

Fig: 5 Comparative Dissolution Profile of Effexor and K15M wet granulation formulations

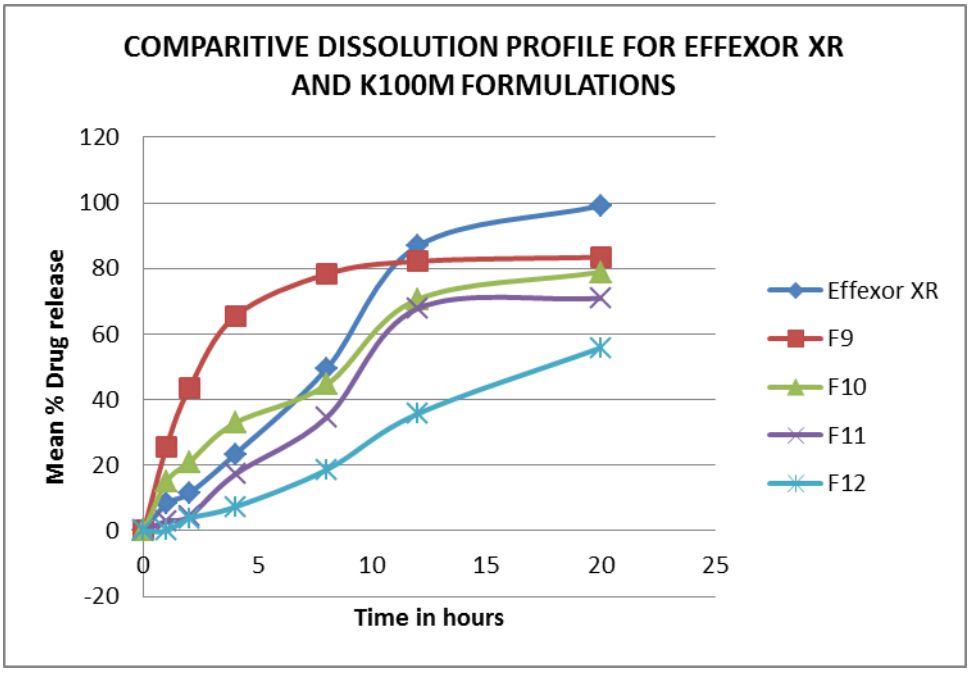

Fig: 6 Comparative Dissolution Profile of Effexor and K100M wet granulation formulations

Formulations Prepared by Dry Granulation Technique

The physical properties of the tablets prepared by direct compression are recorded

Table: 11 Physical properties

FORMULATION CODE	Average weight range (mg)	HARDNESS†(Kg/cm^2)	THICKNESS † (mm)	FRIABILITY† (%) w/w	ASSAY*(%)
F13	902.1±2.13	10.3±0.36	6.53±0.06	0.23	98.04
F14	910.6±4.13	7.1±0.58	6.46±0.04	0.28	97.64
F15	909.5±3.13	8.5±0.63	6.54±0.07	0.32	99.48
F16	908.9±5.83	8.1±0.12	6.80±0.09	0.36	96.00
F17	914.8±6.84	9.8±0.22	6.11±0.06	0.18	98.09
F18	927.7±3.46	8.2±0.54	6.39±0.06	0.29	97.76
F19	914.3±6.22	7.6±0.83	6.86±0.05	0.27	99.84
F20	906.9±5.88	8.2±0.28	6.45±0.03	0.38	96.21
F21	942.2±3.44	7.8±0.62	6.29±0.09	0.27	95.58
F22	913.6±3.99	8.3±0.84	6.73±0.07	0.33	99.87
F23	919.8±4.44	9.6±0.32	6.59±0.01	0.36	97.46
F24	903.2±3.67	7.9±0.21	6.86±0.09	0.27	98.29

*All values are expressed as M ±SE, n=20, † All values are expressed as M±SE, n=10.

The tablets prepared by Dry granulation technique showed hardness in the range of 7 to 10 kg and friability was below 0.3% w/w. All the batches passed the test for assay.

Table: 12 Dissolution Profile for Venlafaxine HCl ER tablets prepared by Direct Compression Method

Time	Effexor XR	k4M %				k15M %				k100 M %			
		15%	25%	35%	45%	15%	25%	35%	45%	15%	25%	35%	45%
	TPP	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24

0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	8.3	35.68	24.56	19.78	15.44	20.21	10.34	7.73	4.55	25.67	9.81	1.84	0
2	11.5	66.89	47.89	35.57	25.43	30.89	17.89	9.68	7.81	46.13	18.59	5.19	2.17
4	23.35	85.8	69.56	60.98	37.81	55.98	47.39	20.41	12.67	64.71	28.47	19.71	11.35
8	49.4	90.1	81.78	87.46	78.63	78.38	70.27	44.97	40.24	78.29	34.59	30.54	19.27
12	86.85	95.57	90.57	98.89	87.57	83.86	80.86	80.16	78.51	82.19	69.16	61.83	31.45
20	99.15	99.47	98.68	99.54	98.54	99.04	97.54	98.97	93.19	87.67	79.37	71.48	63.28

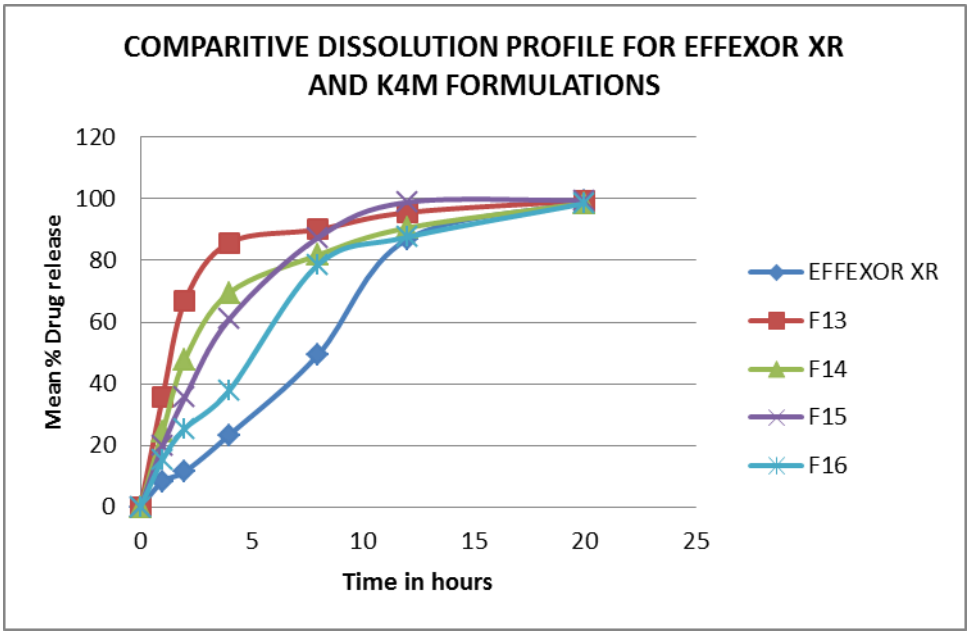

Fig: 7 Comparative Dissolution Profile of Effexor and K4M Direct compressed formulations

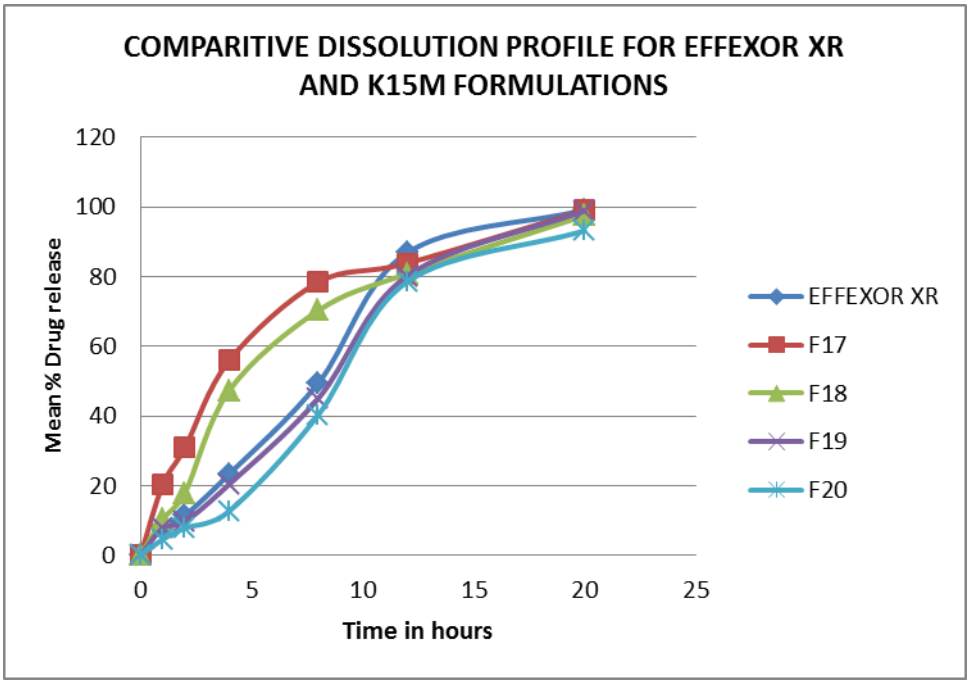

Fig: 8 Comparative Dissolution Profile of Effexor and K15M Direct compressed formulations

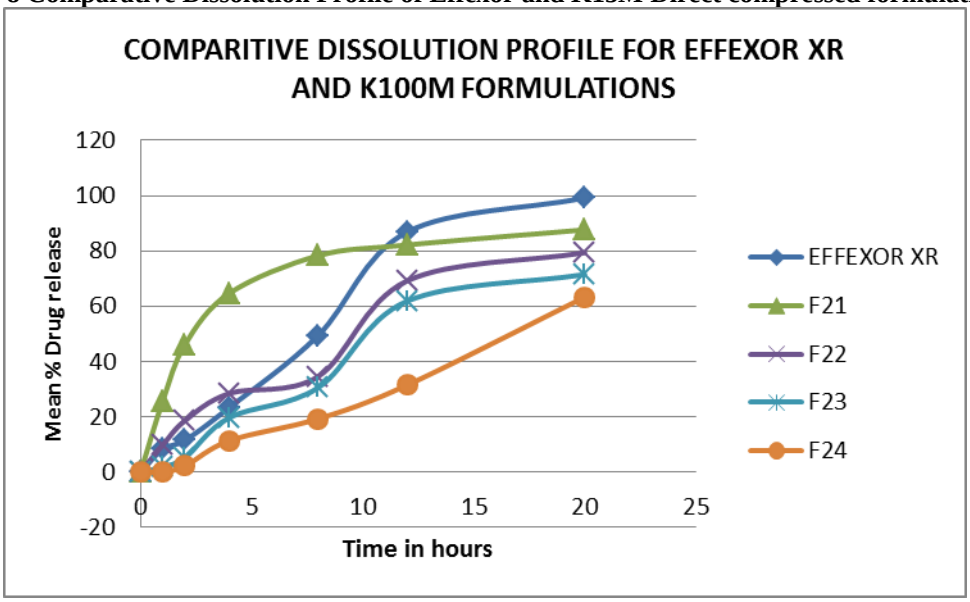

Fig: 9 Comparative Dissolution Profile of Effexor and K100M Direct compressed formulations

From the Dissolution profiles of the 24 formulations, F7 formulation containing K15M 35% prepared by Wet granulation showed better release values to the Targeted product EFFEXOR XR 35mg.

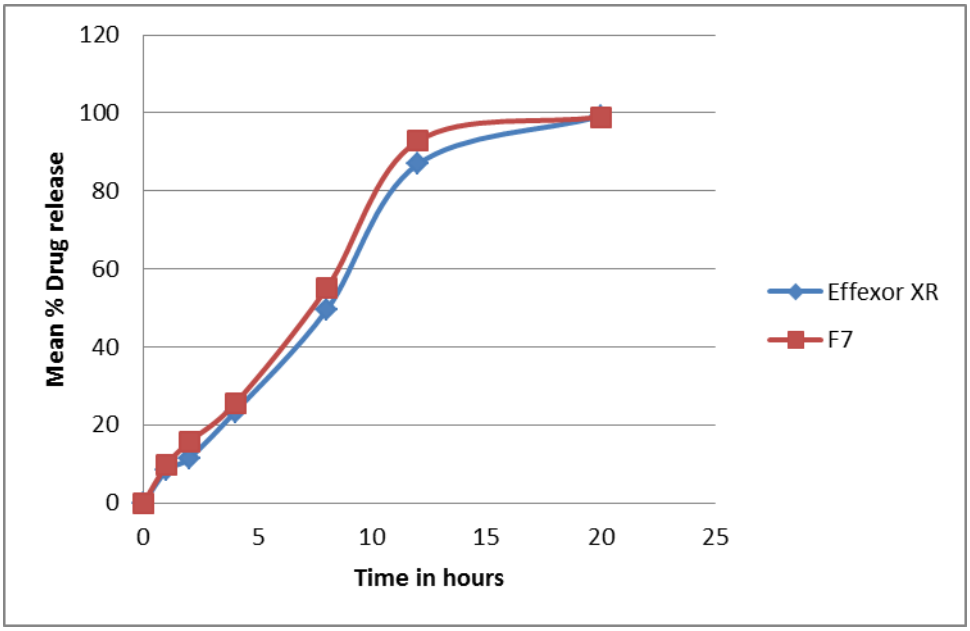

Fig: 10 Comparative Dissolution Profile of F7 with Effexor XR

RELEASE KINETICS OF EFFEXOR XR AND F7 FORMULATION:
Release kinetics of EFFEXOR XR:

Table: Release kinetics of Effexor XR

	RELEASE KINEITCS				
	ZERO	**HIGUCHI**	**PEPPAS**	**FIRST**	**Hixson Crowell**
	1	**2**	**3**	**4**	**5**
	R(CvT)	**R(CvRoot(T))**	**Log T vs Log C**	**TIME vs LOG % REMAINING**	**TIME Vs (Q1/3-Qt1/3)**
Slope	5.344	24.936	0.959	-0.017	0.190
Correlation	0.9718	0.9614	0.9879	-0.9640	0.9880
R 2	0.9444	0.9243	0.9759	0.9293	0.9761

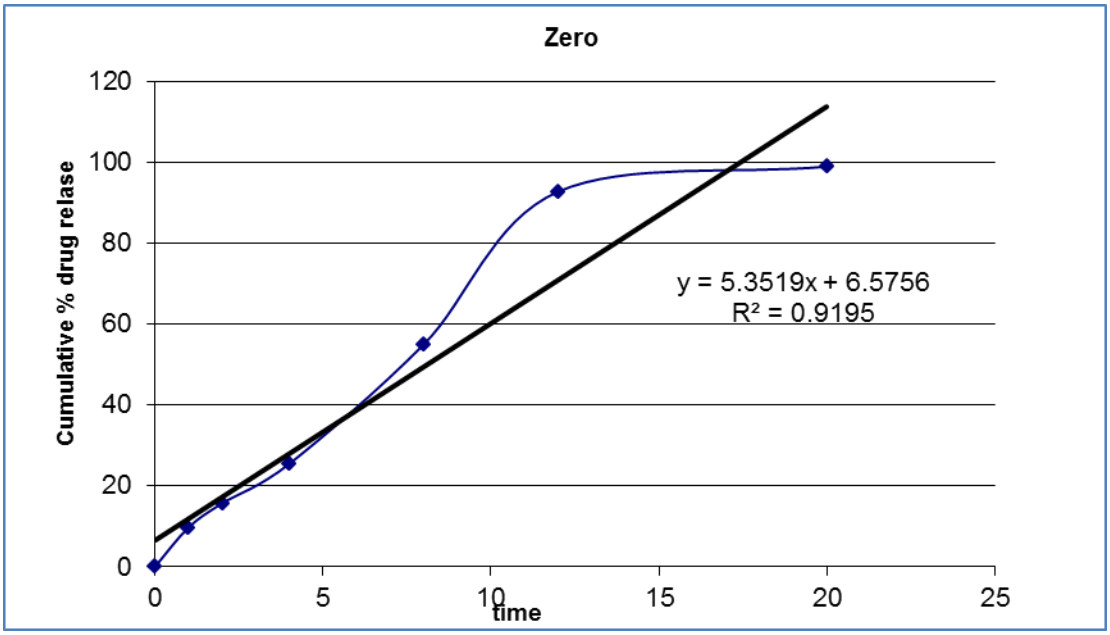

Fig: 11 Zero order plot for Effexor XR

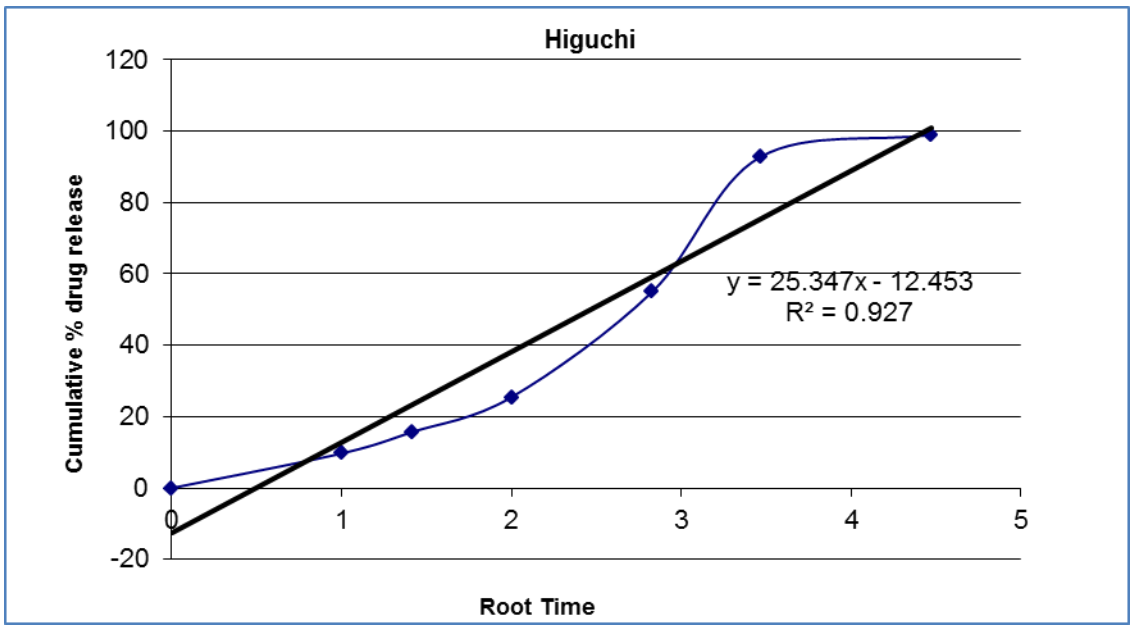

Fig: 12 Higuchi plot for Effexor XR

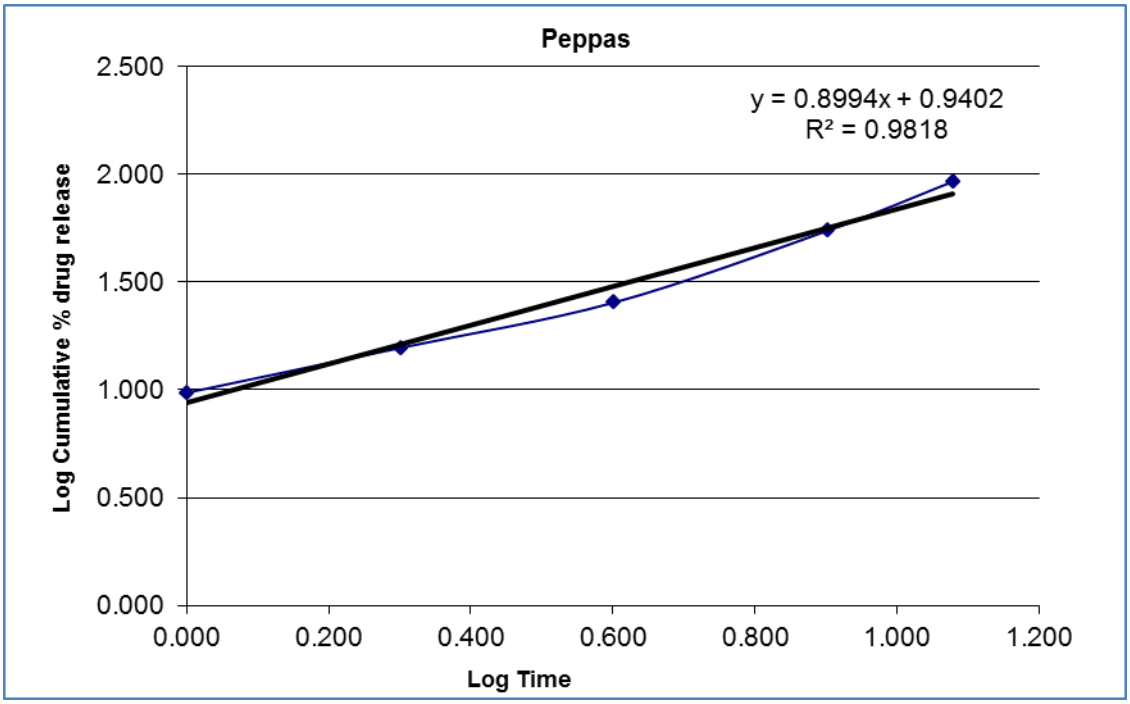

Fig: 13 Peppas plot for Effexor XR

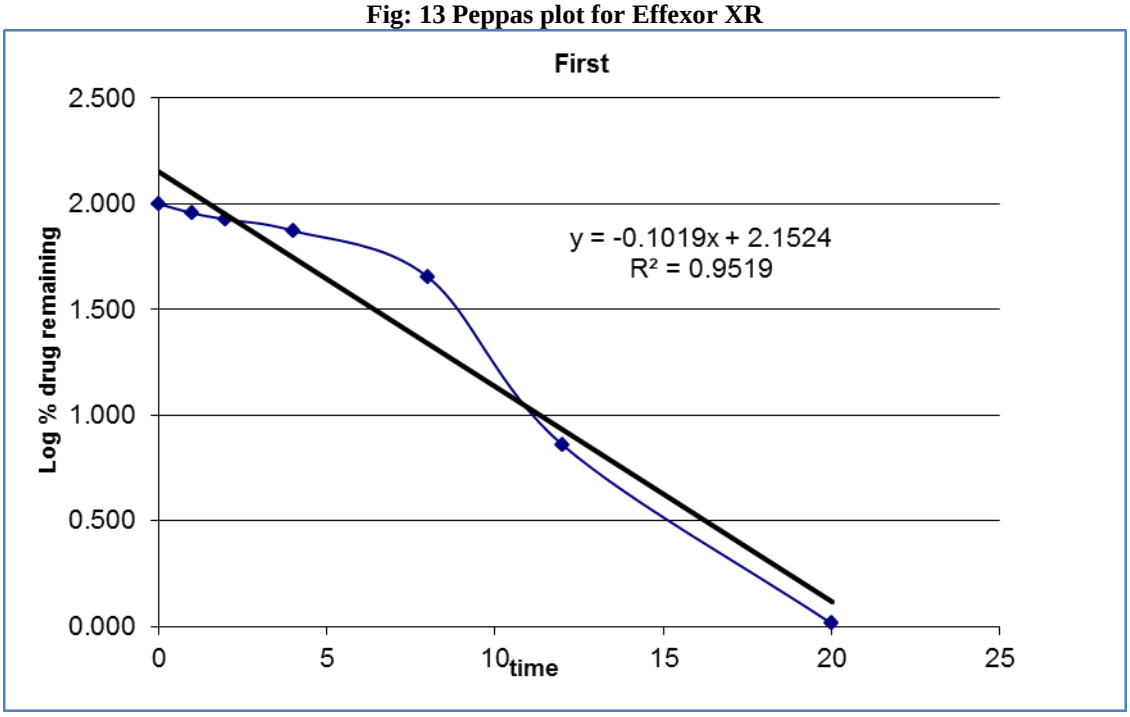

Fig: 14 First order plot for Effexor XR

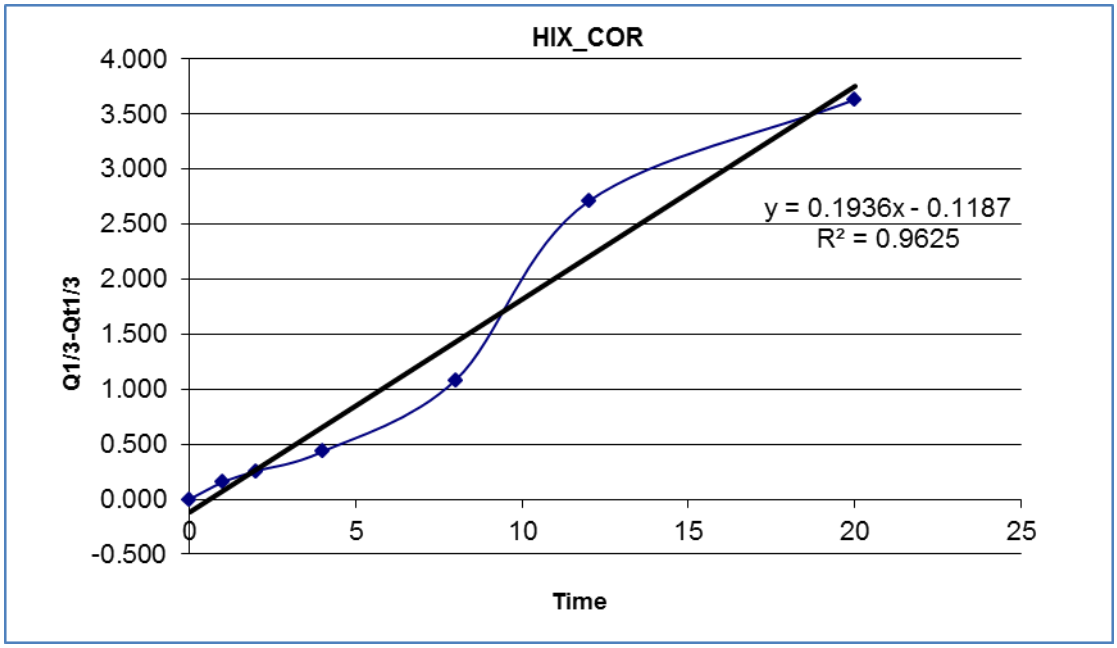

Fig: 15 Hixson Crowell plot for Effexor XR

Release kinetics of F7 formulation:

Table: Release kinetics of F7 formulation

RELEASE KINEITCS					
	ZERO	**HIGUCHI**	**PEPPAS**	**FIRST**	**Hixson Crowell**
	1	**2**	**3**	**4**	**5**
	R(CvT)	**R(CvRoot(T))**	**Log T vs Log C**	**TIME vs LOG % REMAINING**	**TIME Vs (Q1/3-Qt1/3)**
Slope	5.352	25.347	0.899	-0.017	0.194
Correlation	0.9589	0.9628	0.9909	-0.9757	0.9811
R^2	0.9591	0.9270	0.9818	0.9319	0.9625

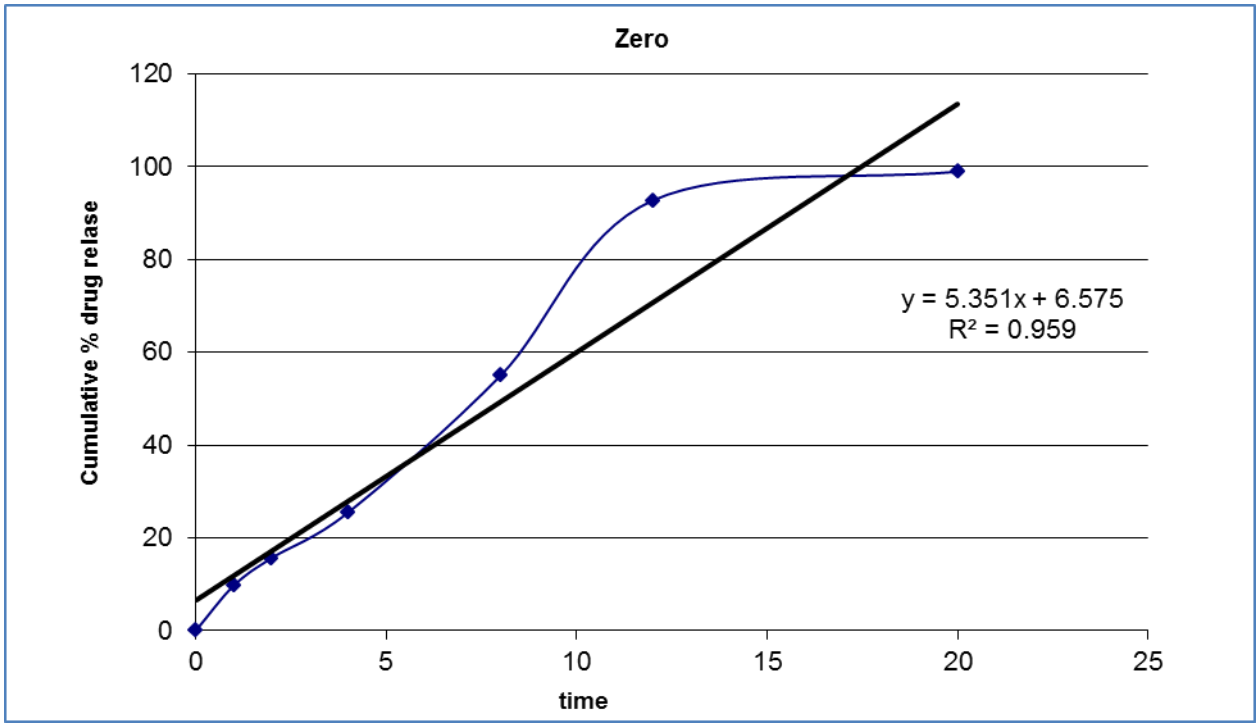

Fig: 16 Zero order plot for F7 formulation

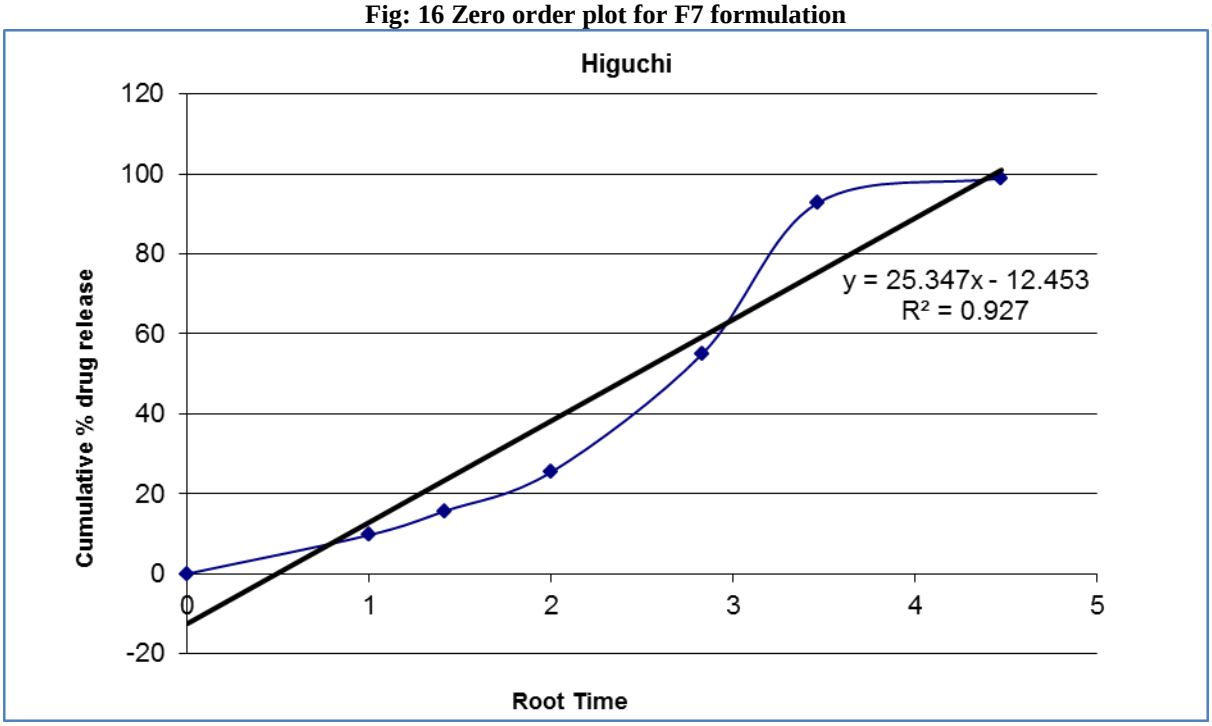

Fig: 17 Higuchi plot for F7 formulation

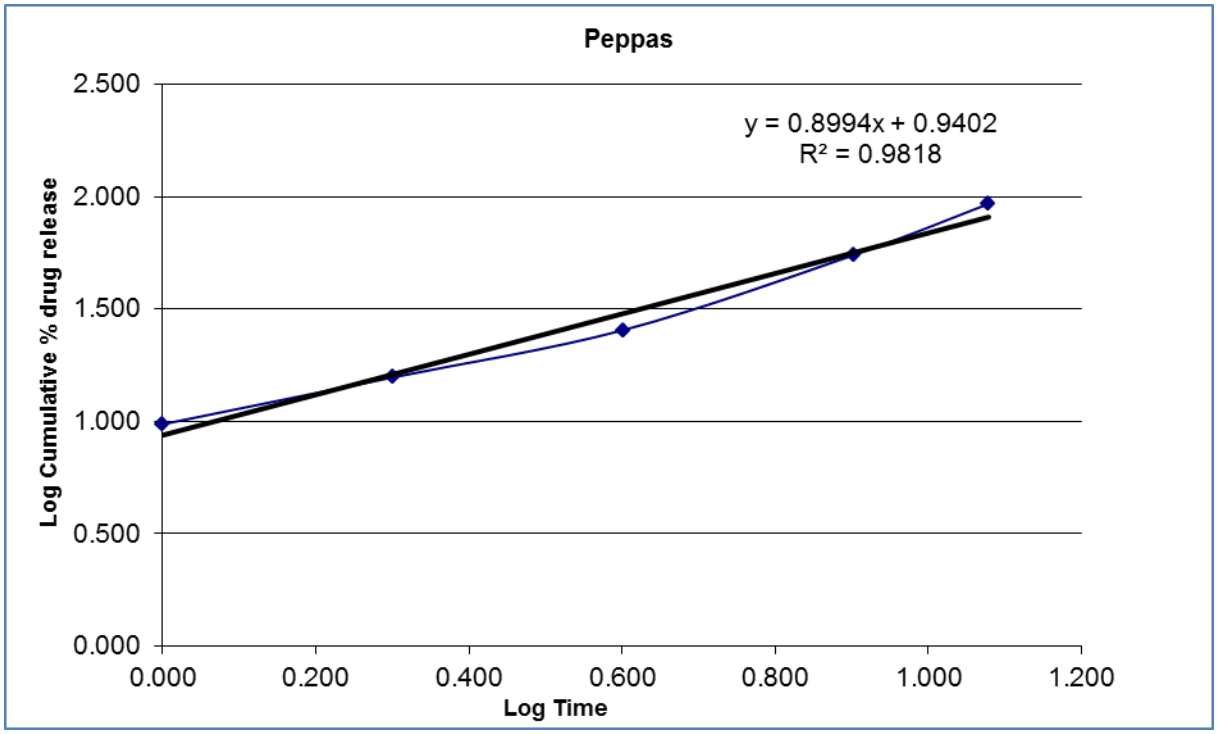

Fig: 18 Peppas plot for F7 formulation

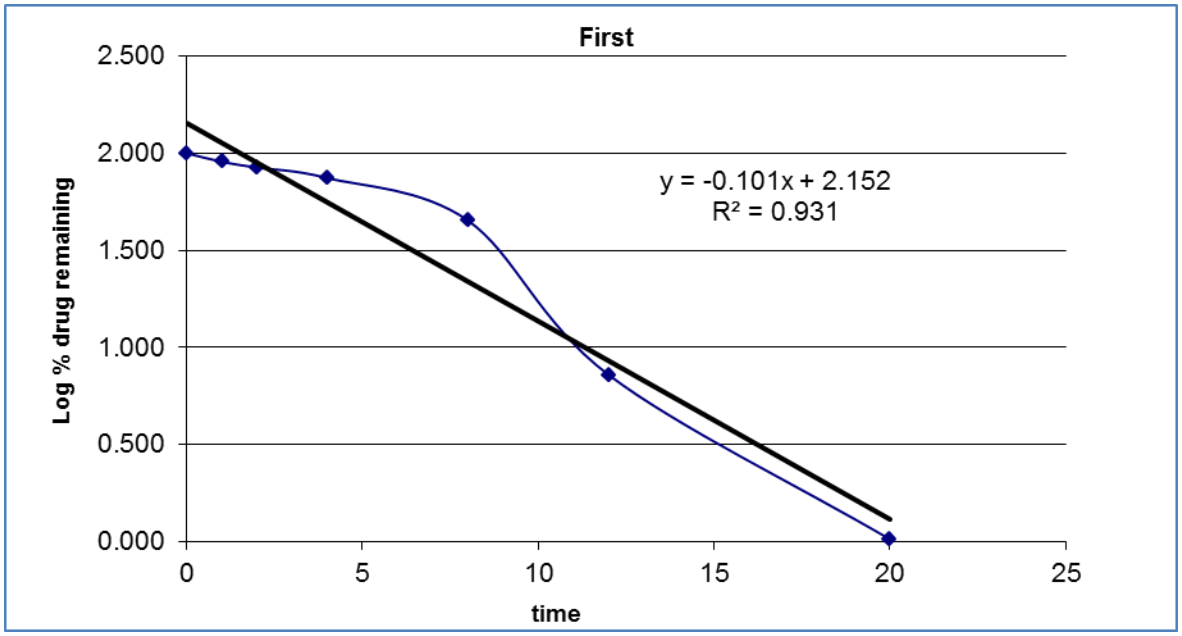

Fig: 19 First order plot for F7 formulation

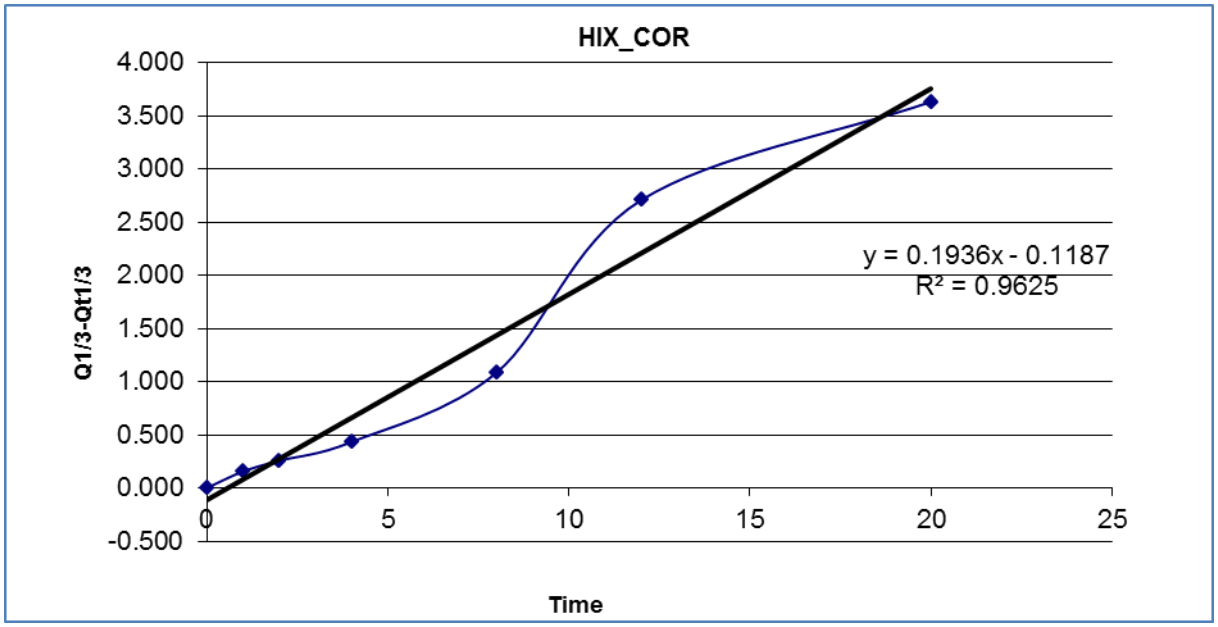

Fig: 20 Hixson Crowell plot for F7 formulation

Comparison of Release kinetics of F7 with EFFEXOR XR:

FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGUCHI		KORSEMEYER -PEPPAS		
	R^2	K	R^2	k	R^2	k	R^2	k	n
EFFEXOR	0.944	5.344	0.929	0.017	0.924	24.93	0.975	0.959	0.987
F7	0.959	5.351	0.931	0.227	0.927	25.34	0.981	0.899	0.940

Kinetic analysis of release data

To understand the rate and mechanism of drug release from optimized tablet formulation, dissolution data was fitted into different release kinetic models. Both the formulations follow Zero order kinetics. The model that best fitted the release data was selected based on the correlation coefficient value (R^2) obtained from various kinetic models. *Invitro* drug release profile from the formulations could be best expressed by Korsmeyer-Peppas equation as plot showed linearity with R^2 value 0.975-0.981. In Korsmeyer-Peppas equation, linear plot was obtained for optimized formulation with more correlation coefficient (R^2) value 0.981 than marketed product. It was concluded that the optimized formulation followed mixed mechanism of diffusion and erosion so called anomalous diffusion mechanism for drug release.

F7 formulation showed better release kinetics than EFFEXOR XR.

VII. Conclusion

The results showed significant effect on the release of drug from the tablets. Formulation F7 was selected as promising formulation and was found that formulation released the drug 90% in 12 hour. From drug release kinetic study we can conclude that optimize batch K15 (35%) is matching the innovator product. This was further concluded from the similarity factor (f2), which was found to be 68.25

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AUTHORS

First Author – K. V. Krishna, Department of Pharmaceutical Technology, Koringa College of Pharmacy (Andhra Pradesh)
Second Author – K. Satyavathi, Department of Pharmaceutical Technology, Koringa College of Pharmacy (Andhra Pradesh)
Third Author – M. Venu, Department of Pharmaceutical Technology, Koringa College of Pharmacy (Andhra Pradesh)