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Formulation and In-vitro comparison of Extended Release Pellets of Venlafaxine with Innovator

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ABSTRACT

The study aims at developing novel extended release pellets of venlafaxine. The main objective of the work was to develop robust extended release formulations of Venlafaxine (test formulation) for regulated markets having comparable in-vitro dissolution profile with Innovator product - Effexor® XR (Reference Product)**.** Venlafaxine spheroids were made using extrusion spheronization technique. The release of the drug from the spheroids was controlled by applying a coating comprising ethyl cellulose as rate controlling polymer. The coated pellets were then encapsulated in the hard gelatin capsules. The *in-vitro* dissolution studies were conducted to evaluate the release of the drug venlafaxine from the coated spheroids contained in capsule at pH 6.8 using phosphate buffer. The in-vitro dissolution profile of the test compositions was compared with Reference Product Effexor XR. The results obtained showed that the test formulations had higher percentage release of venlafaxine in initial time period. Therefore, a better control on the release was desired. During the manufacturing of spheroids, it was observed that more fines were generated during the extrusion spheronization, which is not suitable for large scale production of the formulation. Accordingly batches were optimized using different types of binder and coating composition. Effect of the binder and percentage coating was studied. The drug release of venlafaxine using Povidone K30 as binder, Ethyl cellulose and Acryl-EZE MP 93018508 white as release control polymers was compared with innovator's drug release and was found to be equivalent. From the results, it was concluded that use Povidone K30 as binder during extrusion spheronization process results on generation of less fines, thus increases the yield of the product. Also, the formulation containing dual coating of Ethyl cellulose and Acryl-EZE MP 93018508 on the spheroids containing Povidone K30 as binder showed the dissolution profile similar to that of the Reference Product Effexor XR.

Keywords: Venlafaxine, Ethyl Cellulose, Povidone K30, Acryl-EZE, USP-I Apparatus.

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INTRODUCTION

Effexor XR is an extended-release capsule for oral administration that contains venlafaxine hydrochloride, a structurally novel antidepressant. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α- [(dimethylamino)methyl]-pmethoxybenzyl]cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ HCl. Its molecular weight is 313.87. The structural formula is shown below[1]

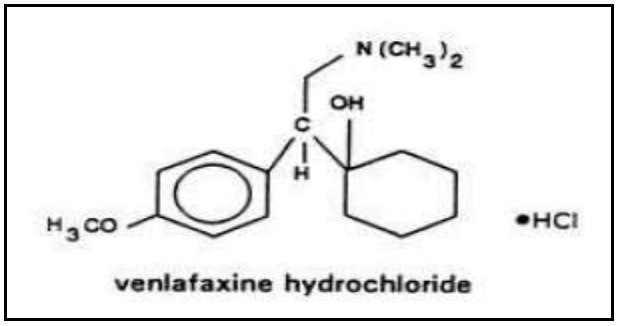

Figure 1: Structure of venlafaxine

Venlafaxine is used primarily for the treatment of depression, general anxiety disorder, social phobia, panic disorder and vasomotor symptoms. At low doses (<150 mg/day), it acts only on serotonergic transmission. At moderate doses (>150 mg/day), it acts on serotonergic and noradrenergic systems, whereas at high doses (>300 mg/day), it also affects dopaminergic neurotransmission[2].

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol: water (0.2 M sodium chloride) partition coefficient is 0.43.

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of cellulose, ethyl cellulose, gelatin, hypromellose, iron oxide, and titanium dioxide [2]

First introduced by Wyeth in 1993, now marketed by Pfizer, it is licensed for the treatment of major depressive disorder (MDD), as a treatment for generalized anxiety disorder, and comorbid indications in certain anxiety disorders with depression. In 2007, venlafaxine was the sixth most commonly prescribed antidepressant on the U.S. retail market, with 17.2 million prescriptions.[3] Venlafaxine is used primarily for the treatment of depression, general anxiety disorder, social phobia, panic disorder and vasomotor symptoms.[4]

Bagdiya et al. discloses formulation and development of Venlafaxine hydrochloride extended release pellets by extrusion spheronization method using combination of hydrophobic low melting wax and hydrophilic polymers as release retarding agent.[5] Krishnarajan et al. discloses sustained release capsules of Venlafaxine hydrochloride were formulated by using the pelletization process by drug layering on inert sugar pellets by using sucrose and Hypermellose 606 as a binder.[6] Remya et al. discloses formulation and performed in-vitro characterization of sustained release pellets of Venlafaxine hydrochloride by wruster process technique.[7] Kumar et al. discloses preparation of venlafaxine extended release pellets by extrusion spheronization technology, coating them with mixture of rate controlling polymers ethyl cellulose and different grades of (Hydroxy propyl methyl cellulose (HPMC)) using Wurster process.[8]

MATERIALS AND METHODS

Materials:

Venlafaxine (Wockhardt Research Centre, Aurangabad). All reagents and chemicals were of analytical grade. All excipients used were GRAS listed and within iig limits.

Method:

The formulation development for test formulation comprising Venlafaxine Hydrochloride Extended Release 37.5 mg, 75 mg, and 150 mg was aimed at developing a stable and robust extended release formulation of Venlafaxine Hydrochloride, which has similar in-vitro dissolution to the reference listed drug (RLD) Effexor ER® 37.5 mg, 75 mg, and 150 mg (Venlafaxine Hydrochloride Extended Release Capsules 37.5 mg, 75 mg, and 150 mg) by Wyeth Pharma Inc. in terms of active drug substance, dosage form, route of administration, usage and indications and is also equivalent in term of in-vitro drug release profile.

Innovator Product Evaluation

Table 1: Characterization of innovator product

Innovator Product Name	**Effexor XR®**		
Strength	**37.5 mg**	**75 mg**	**150 mg**
Description	Grey cap/peach body with W and "Effexor XR" on the cap and "37.5" on the body containing spheroids	Peach cap and body with W and "Effexor XR" on the cap and "75' on the body containing spheroids	Dark orange cap and body with W and ".Effexor XR" on t11e cap and "150" on the body containing spheroids
Average fill weight	125.24 mg	247 mg	500 mg
Inactive ingredient	Cellulose, Ethyl cellulose, Gelatin, Hypromellose, Iron oxide, and Titanium dioxide		

Preliminary evaluation of reference listed product (Effexor® ER 37.5 mg, 75 mg, and 150 mg by Wyeth Pharma Inc.) was carried out for physical characterization (average weight and description) and multimedia drug release profiles were performed. The data has been tabulated below:

Formulation Strategy:

Based upon the characterization of the Effexor XR® Capsules, it was determined that the generic formulation would be having following characteristics.

- Formulation in a capsule dosage form to be pharmaceutically equivalent to Effexor XR (RLD Reference listed drug)
- Capsule will be filled with coated pellets since the RLD contain spheroids and also as indicated in RLD labeling
- Drug release profile to be extended over a period of 24 hours as per RLD's release profile and labeling

Extrusion and Spheronization technique was used to prepare the spheroids. These spheroids were coated with ethyl cellulose as release controlling polymer and Triethyl citrate as plasticizer. Ethyl cellulose forms an insoluble and semi permeable membrane coating and the drug release from the pellets coated with ethyl cellulose polymer could be by diffusion mechanism. These coated pellets were then encapsulated in the hard gelatin capsules.

The basic scheme is as presented as follows:

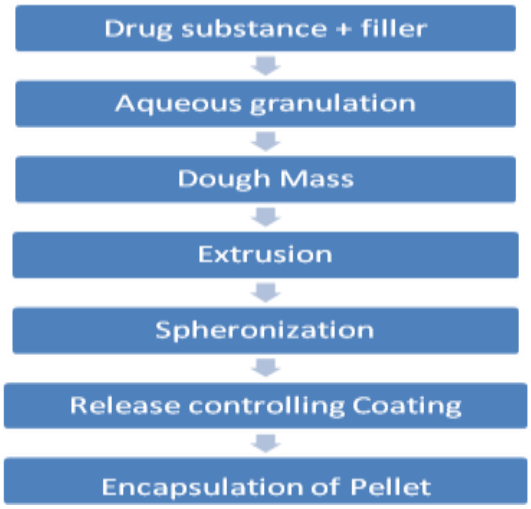

Figure 2: Scheme of Pelletization

Dissolution Testing Methodology:-

The following dissolution method was adopted initially for prototype development for the Venlafaxine Hydrochloride Extended Release Capsules

Table 2 Dissolution parameters

Dissolution Media	pH 6.8 Phosphate Buffer
Volume	900mL
Apparatus	Type I (Basket)
RPM	100
Sampling Time Points	1, 2,4,6,8,12,16,20 and 24 Hours

Above dissolution method was finalized since the capsules float when placed in the dissolution media, so USP-I apparatus with 100 rpm (standard) was selected. Secondly, since it is a multiparticulate formulation and gastric empting time is around 1-2 hours, the extended release coated pellets capsules may reach the intestine where pH is around 6.8 to 7.2. Hence, pH 6.8 buffer was selected.

Also, since it is extended release formulation and innovator drug release profile is also upto 24 hours in all the media, majority of the drug release will be there in small and large intestine. Further, as per the innovator labeling also (pK data), Tmax of Venlafaxine Hydrochloride is around 6-8 hours. Sampling points as mentioned above were selected so as to monitor dose dumping, optimum and complete drug release. Hence the above method was selected during drug development.

Prototype Development:

Venlafaxine Hydrochloride Extended Release Capsules, 150 mg

Venlafaxine Hydrochloride was mixed with Microcrystalline Cellulose (Avicel PH 101) and granulated with Purified water. This mass was passed through extruder with 1.0 mm. aperture size drum with knife. Extruded mass was then spheronized in the spheronizer for 15-20 minutes till the beads became spherical, Further these were dried in fluid bed dryer and the # 12/25 mesh fraction of beads was collected.

The # 12/25 mesh pellets were coated with coating dispersion of Ethyl cellulose and Triethyl Citrate as plasticizer in a mixture of Methylene chloride and isopropyl alcohol (80:20 ratios).

Batch number VERC-39A/05: Spheroids were coated in Fluid bed Processor (GPCG 5) using 1 mm spray nozzle to a weight gain of 8.5 %w/w. Samples of 7.5%w/w were also evaluated for the drug release profile in pH 6.8 phosphate buffer, 900 mL, USP type- I, at 100rpm.

Batch number VERC-39B/05: Spheroids were coated in Fluid bed Processor (GPCG 5) using 1 mm spray nozzle to weight gain of 10 % w/w. Samples of 8% and 9% w/w weight gain were also evaluated for the drug release profile in pH 6.8 phosphate buffer, 900 mL,

Prototype Development with inclusion of Additional Extended Release Coating II:

For achieving a better control over the release of the drug from the spheroids and to ensure a

robust release controlling system for delivering the drug in intestine, the spheroids were additionally coated (Extended release coating –II) with an acrylic polymer (Acryl EZE MP).

Prototype development with inclusion of binder:

Batch was fabricated using hypromellose 6 cps (Methocel E6) as binder at 1% w/w

Table 3: Hypromellose as binder

S.No	Ingredients	150mg capsules
Core Spheroid		
1	Venlafaxine Hydrochloride	169.738
2	Microcrystalline cellulose	149.00
3	Hypromellose 6cps{HPMC E6)	3.20
Total		

Procedure:

Venlafaxine Hydrochloride was mixed with Cellulose, microcrystalline (Avicel PH 101) and Hypromellose 6 cps. After granulation with Purified water, this mass was passed through extruder with 1.0 mm aperture size drum with knife. The extruded Mass was then spheronized in the spheronizer for 5-10 minutes till the beads become spherical and were further dried in fluid bed dryer. Pellets from the #12/30 mesh fractions were collected for coating.

Povidone K30 as binder

Another batch was planned including Povidone K30 as binder for the preparation of spheroids. Weight gain of extended release coating I was reduced to 7.0%w/w.

Table 4: Venlafaxine Hydrochloride Extended Release Capsules (150 mg)

S. No	Ingredients	mg/capsules	% w/w
Core Spheroid			
1	Venlafaxine Hydrochloride	169.738	48.33
2	Cellulose, microcrystalline (Avicel PH 101)	148.86	42.39
3	Povidone K30	3.20	0.91
4	Purified water	q. s.	--
Extended Release Coating I			
5	Ethylcellulose	20.478	5.83
6	Triethyl citrate	2.048	0.58
7	Methylene chloride	496.85	--
8	Isopropyl alcohol	124.21	--
Extended Release Coating II			
9	Acryl EZE MP white 93O18508	6.886	1.96
10	Purified water	q. s.	--
Lubrication			
11	Talc	0.7	0.2
Average Fill weight (spheroids)		351.21	100

Procedure:

Venlafaxine Hydrochloride, Cellulose, microcrystalline (Avicel PH 101) and Povidone K30 were sifted through #20 mesh and mixed in the rapid mixer granulator for 5 min at slow speed and the mass was granulated by adding Purified water. The wet mass was extruded using drum extruder at 75 rpm and spheronized in spheronizer at 1000 rpm for 4-6 minutes. The spheroids were dried in FBD at 60±5ºC. The dried spheroids were coated with the coating solution I of Ethylcellulose and Triethyl Citrate in Isopropyl alcohol and Methylene chloride. The weight gain of extended Release Coating -I was 7.0%w/w. Coating II of Acryl EZE MP White 93O18508 was carried out with weight gain of 2.0%w/w. Final coated spheroids were lubricated with the 0.2% talc and encapsulated in the hard gelatin capsules size "0". Multimedia drug release profiles were carried out in 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

RESULTS AND DISCUSSIONS:

Multimedia drug release profiles were carried out in 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The drug release was high in 6.8 buffer compared with other medium.

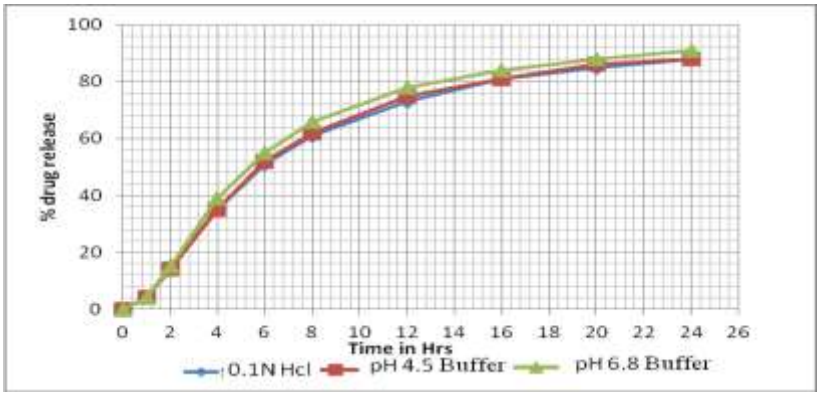

Figure 3: Dissolution release profile of Effexor^{XR} Capsules, 150 mg

Table 5: Drug Release profiles of Effexor^{XR} Capsules, 150 mg

Volume of Media: Apparatus:	**900 mL, USP type: l, 100 rpm, Mean % .Drug Release**		
Time in Hours	**0.1 N HCl**	**pH 4.5 Acetate Buffer**	**pH 6.8 Buffer Phosphate**
0	0	0	0
1	4	4	4
2	15	14	15
4	35	35	39
6	51	52	55
8	61	62	66
12	73	75	78
16	81	81	84
20	85	86	88
24	88	88	91

The release of Effexor XR dissolution results were shown in graph 3

Comparison of venlafaxine pellets was carried out with innovator and their in-vitro drug release profiles was carried out their release was shown in table 6 and release was shown in fig 4.

Table 6: Comparison of Drug release profile of development batches vs. Effexor XR®

Apparatus		**pH 6.8 phosphate buffer, 900 mL, USP type-I, 100 rpm**	
		Mean % Drug Released	
		7.5% w/w	**8.5% wlw binder**
0	0	0	0
1	4	12	8
2	15	31	25
4	39	48	42
8	61	66	60
12	73	76	72
16	81	83	78
20	85	87	84
24	88	91	88

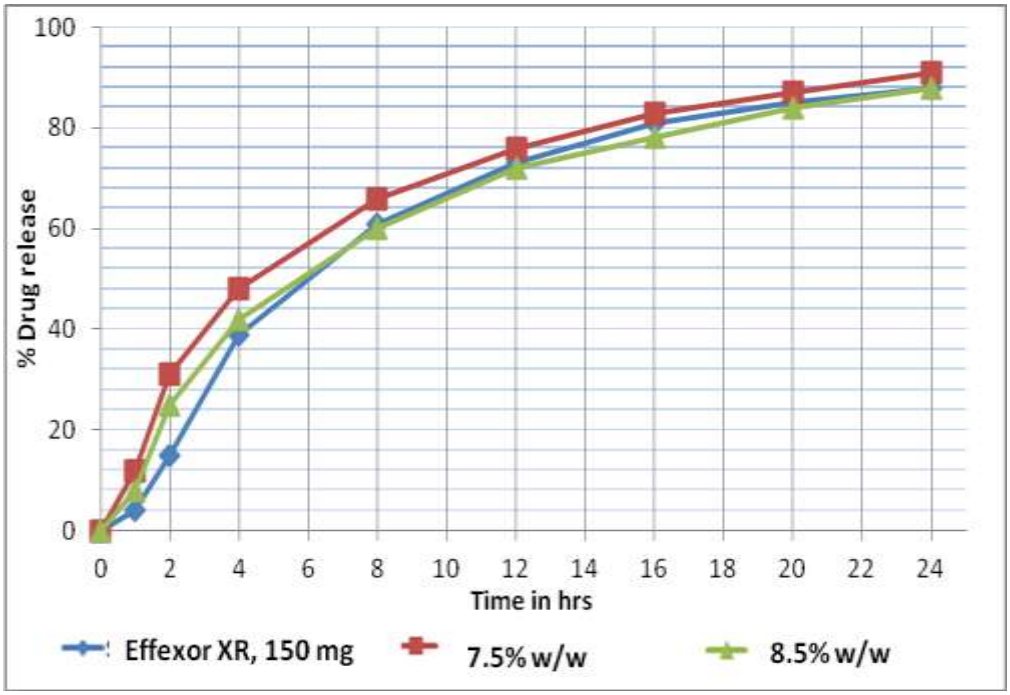

Figure 4: Dissolution release profile

On increasing the percentage coating of the ethylcellulose polymer from 7.5%w/w to 8.5%, better control from the initial release of the drug from the spheroid was obtained but no significant difference in % drug release from the spheroid was observed after 12h. Therefore, percentage coating weight gain has no significant effect on drug release.

Table 7: Comparison of Drug release profile of development batches vs. Effexor XR®

Volume of Media, Apparatus		**pH 6.8 phosphate buffer, 900 mL, USP type-I, 100 rpm**		
	Mean % Drug Released			
Time in Hours	**Effexor XR, 150 mg**	**Batch Number: VERC-39B/05**		
		(Coating Weight Gain)		
		8%w/w	**9%w/w**	**10% w/w (Selected for developmental BE studies)**
0	0	0	0	0
1	4	9	7	7
2	15	23	20	18
4	39	41	37	36
8	61	58	55	53
12	73	69	64	64
16	81	77	72	71
20	85	82	77	77
24	88	88	82	81

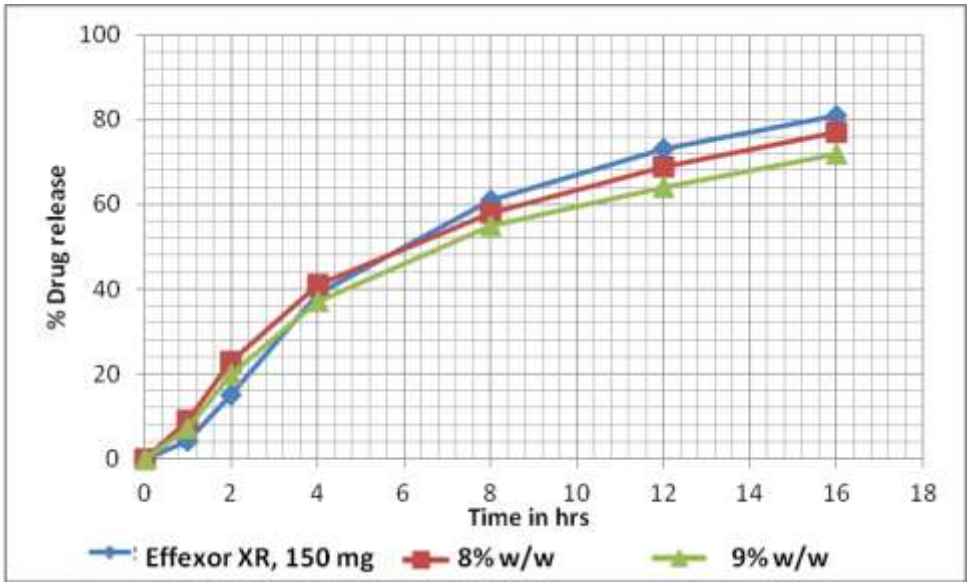

Figure 5: Dissolution release profile

Prototype development with inclusion of binder:

Hypromellose as binder

Result:

The pellets collected from the #12/30 fraction were only 55% and pellets retained over #12 mesh were 44%.

Discussion:

Batch was not further processed as the yield of the desired fraction of pellets was low.

Povidone K30 as binder

Results:

Table 8: Comparison of Drug release profile of development batches vs. Effexor® XR

Time (hr)	Volume of Media Apparatus Mean % Drug Released		900mL USP type-1, 100 rpm			
	0.l NHCI		pH 4.5 Acetate Buffer		pH 6.8 Phosphate Duffer	
	Effexor XR 150	USB(113)-45-01	Effexor XR 150	USB(113)-45-01	Effexor XR 150	USB(113)-45-01
0	0	0	0	0	0	0
1	4	9	4	11	4	9
2	15	20	14	23	15	21
4	35	38	35	40	39	38
6	51	50	52	50	55	51
8	61	59	62	57	66	61
12	73	71	75	68	78	73
16	81	80	81	75	84	82
20	85	86	86	80	88	88
24	88	91	88	83	91	93

Discussions :

Batch size was 3000 capsules. Bulk density of premix was 0.16 g/cc. Premixing conditions: 5 minutes, slow impeller and chopper off and subsequent granulation for 1 minute with impeller and chopper at slow speed. Drug release profile of the finalized formulation is comparable with the innovator in all three media.

CONCLUSION:

The novel extended release pellets of venlafaxine hydrochloride were formulated using ethyl cellulose and acryl-EZE as rate controlling polymers. The release was found to be similar to the RLD but the yield of the spheroids was very poor because of generation of more fines, different binders were tried like Hypromellose and Povidone K30 out of which Povidone K30 was found to be suitable. The formulations with Povidone K30 as binder decreased the generation of fines thereby increasing the yield of the spheroids. Also the formulation comprising Povidone K30 results in a release profile similar to that of RLD. On increasing the percentage coating of the ethylcellulose polymer from 7.5%w/w to 8.5%, better control from the initial release of the drug from the spheroid was obtained but no significant difference in % drug release from the spheroid was observed after 12h. Therefore, percentage coating weight gain has no significant effect on drug release. When an additional coat of acrylic acid polymer was added to the extended release formulation coated with ethylcellulose polymer, the percentage weight gain for ethylcellulose was kept at 7%w/w and an additional coat of 2%w/w of acryl-EZE was applied. Thus, the pellets

were prepared using the above mentioned rate controlling polymers and binder. The *in-vitro* dissolution profile of the pellets was found to be similar to the Reference Product.

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