International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

FORMULATION DEVELOPMENT OF VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE PELLETS BY EXTRUSION SPHERONIZATION METHOD

Omprakash Bagdiya, Ajay Kumar Sav* and Purnima Dhanraj Amin

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai- 400 019, Maharashtra, India

***Corresponding author e-mail:** aksav.ict@gmail.com

ABSTRACT

Venlafaxine hydrochloride is an antidepressant drug used to treat various mental disorders. Single layer or double layer coating generally used method to prepare extended release pellets of Venlafaxine hydrochloride. In current work, extended release pellets of Venlafaxine was prepared by extrusion spheronization method using combination of hydrophobic low melting wax and hydrophilic polymers as release retarding agent. This method avoids the process of layering or film coating. The optimized capsule formulation containing Venlafaxine hydrochloride pellets (F10) was evaluated for physical properties like size distribution, surface morphology and *Invitro* drug release. The developed capsule formulation was found to be complying with the marketed formulation Venlor XR ® (37.5 mg) with respect to dissolution *Invitro* drug release profile and physical property. SEM study showed that formulation comprised of sphere pellets of uniform size. Dissolution data was found to be best fitted in Higuchi equation revealed that drug releases by diffusion mechanism. The optimized batch (F10) was found to be stable for period of stability study.

Keywords: Venlafaxine, pellets, extrusion spheronization, release kinetic

INTRODUCTION

For pharmaceutical applications, pellets are defined as spherical, free-flowing granules with a narrow size distribution (500-1500 µm). [1] The ultimate dosage forms for pellets can be capsule or compressed into disintegrating tablets and interest in this area has been increasing continuously, since it offers some important pharmacological as well as technological advantages [2]. The aim of present study was to develop extended release pellets formulation of Venlafaxine hydrochloride as it has several advantages over conventional dosage form like reduced dosing frequency, maintenance of plasma drug levels, reduced adverse effect and improved patient compliance [3]. Extrusion spheronization method was adopted for the preparation of venlafaxine extended release pellets. Extrusion spheronization is defined as a process in which a wet mass was extruded through a specific sieve having fixed diameter and spheronized into spherical particle called as spheroids, pellets, beads or matrix pellets depending upon materials and process used for extrusion spheronization [4].

Venlafaxine is drug of choice for patients suffering from major depression and agitated or retarded symptoms and treatment-resistant depression. Mechanism of action involves inhibition of neuronal uptake of neurotransmitter like nor epinephrine, serotonin and dopamine. Owing to its low affinity towards brain muscarinic, cholinergic, histaminergic or alpha adrenergic receptors and no MAO inhibitory activity, it lacks the adverse effects associated with other tricyclic antidepressants like anticholinergic, sedative and cardiovascular effects [5, 6]. Short biological half life drug also favors the formulation extended release dosage form.

In literature, Venlafaxine SR pellets has been prepared using wax like materials as a release retardant [7], extended release pellet formulation for

24h using hydroxyl propyl methyl cellulose and ethyl cellulose as film coating material to retard the drug release [8], Venlafaxine SR pellets prepared by double layer coating with cestostearyl alcohol and acrylates based polymer[9], extended release pellets in a capsule comprise of immediate release and extended release pellets unit[10], matrix pellets of Venlafaxine was prepared by extrusion spheronization method using ethyl cellulose and HPMC [11], pellets prepared by combination of wax matrices and double layer coatings [12] has been reported.

The objective of present research work was to develop extended release capsule formulation containing Venlafaxine hydrochloride pellets by simple laboratory scale extrusion spheronization method which can be easily scaled up in industry.

MATERIALS AND METHODS

Materials: Venlafaxine Hydrochloride was obtained as a gift sample from Amoli Organics Pvt. Ltd. (Vadodara, India). Hydrogenated soybean castor oil (Sterotex® K, Abitec group, Mumbai. India), Glyceryl behenate/Glycerol dibehenate (Compritol ® 888ATO - Gattffosse, France), Glyceryl distearate (Precirol® ATO 5- Gattffosse, France), Glyceryl mono stearate (Capmul®- Abitec group), Hydroxy propyl methyl cellulose (Methocel® K4M, Methocel® K15M and Methocel® K100M – Colorcon Asia Pvt. Ltd, India), Poly ethylene oxide (Polyox® WSR303, Dow Chemical Corporation, Midland MI) and Micro crystalline cellulose (Avicel® PH101 - Signet chemical corporation, Mumbai, India).

Methods

Preparation of extended release Venlafaxine hydrochloride pellets: The compositions for all the batches are given in Table 1. All the ingredients including drug and polymers were weighed accurately, sieved through 40 mesh sieve and mixed geometrically in a mixing bag. Powder blend was granulated with purified water and IPA mixture (50: 50) to form wet mass. This wet mass was then extruded manually through in house developed axial type single screw extruder having 1 mm extruder screen (Figure 1). Extrudate was then spheronized using a Spheronizer S - 150, equipped with a 2 mm friction plate at 600 rpm for 7 min. Spheronized pellets were dried in a drying oven at 60°C for 4 h. These dried pellets were screened through 18, 30 and 40 mesh and pellets retained on 40 mesh were filled in size one hard gelatin capsule and stored till further evaluation.

DRUG-EXCIPIENTS INTERACTION

***FTIR spectroscopy study*:** To investigate the drug and excipients interaction, FTIR and DSC study was performed. FTIR spectra for drug and drug excipients mixture was recorded using PERKIN ELMER FTIR spectrophotometer (Spectrum RX1, USA).Scanning range was 500 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential Scanning Calorimetry (DSC): DSC analysis was performed using PERKIN ELMER DSC Pyris-6 (USA). A weighed amount of sample (2-6mg) was heated in an sealed aluminum pan at a rate of 10°C / min within a 30 to 300°C temperature range under a nitrogen flow of 20 ml/min. An empty sealed pan was used as a reference. Presence of any changes in FTIR spectra or DSC thermogram , an indication of chemical interaction between drug and excipients.

PHYSICAL CHARACTERIZATION OF PELLETS

Particle size distribution study: Particle size distribution study was performed by mechanical sieve analysis method. For this, different mesh size sieves like 18, 20, 30 and 40 mesh has been used. Pellets were shaken for 10 min by holding the sieves in a series such that 18 mesh remains at top and 40 mesh at the bottom. Percentage retained particles on each sieve calculated.

Scanning electron microscope (SEM)*:* Scanning electron microscopy was performed on extruded pellets of Venlafaxine hydrochloride to assess the surface morphology like size and shape. Sample was fixed on an aluminum stub with conductive double sided adhesive tape and coated with gold in an argon atmosphere (50 Pa) at 50mA for 50 s. The samples were scanned at a voltage of 5kV (JEOL JSM-680 LA 5KV-Japan).

Drug content analysis*:* Three capsules containing Venlafaxine hydrochloride was crushed to a fine powder. A weighed quantity of powder (100mg) was taken into a 100 ml volumetric flask for drug content analysis using purified water as extracting solvent. Drug was extracted for 2h in a shaker bath. Volume was made to 100ml to get clear solution. This solution was filtered through Whatman filter paper No. 41 and required dilution was made. Drug content was analyzed by using double beam UV-spectrophotometer 1600 (Shimadzu, Japan) at 226 nm. The drug content was calculated using the standard plot concentration vs. absorbance. Analysis was done in triplicates.

***Invitro drug release study*:** *In vitro* dissolution testing of Venlafaxine hydrochloride extended release capsule was performed using a USP apparatus I (Basket) Electrolab, India. The dissolution medium consisted of 900 ml of purified water. Dissolution was performed at 37±0.5°C, with stirring speed of 100 rpm. 10 ml of aliquot was withdrawn at time intervals of 2, 4, 8 and 12 h. The medium was replenished with same amount of fresh purified water each time. The samples were analyzed by UV Spectrophotometer at 226 nm. Marketed formulation Venlor® -XR (37.5 mg) was also evaluated for *invitro* drug release.

Mathematical model fitting of Invitro drug release: To analyze the mechanism of drug release from the various batches, obtained dissolution data was fitted to zero order, first-order, Higuchi, Hixon-Crowell, Korsemeyer and Peppas equations [13-17]. Zero order equation describe the systems where the drug release rate is independent of concentration of the dissolved substance, first order release equation describe the rate of drug release depends on its concentration, Hixon-crowell equation describes the drug release by dissolution and with the changes in surface area and diameter of the particles or tablets, Higuchi equation suggests that the drug releases by diffusion mechanism. Peppas equation was used when the release mechanism is not well known and more than one type of release is observed.

Similarity factor: Similarity factor value was calculated for marketed formulation Venlor® XR and developed optimized batch using the formula, $f_2=50 \log \{[1+ (1/N) \Sigma (Ri -Ti)^2]^{-0.5} X100\}$, where N is number of time points, Ri and Ti are dissolution of reference and test products at time i respectively. F2 values greater than 50 considered as two products are similar and showed similar drug release profile.

Stability study: The optimized capsule formulation (F10) was packed in high density polyethylene bottle and subjected to stability studies at 40°C± 2 °C/75±5% RH for three months. Sample was withdrawn at predetermined time and evaluated for drug content and in vitro release.

RESULTS AND DISCUSSION

Drug excipients interaction: Venlafaxine HCl showed a characteristic stretching band of aromatic C=H at 1609cm^1 , O-H showed stretching vibration at 3500 cm^{-1} , C-O stretching was observed at 1500 cm^{-1} and C-N stretching at 1176 cm^{-1} wave number as shown in Figure 2. FTIR spectra of pellets showed absence of some of the original functional group of drug, indicating chemical interaction between drug and polymers but DSC thermogram (Figure 3) obtained for pellets showing similar endothermic peak corresponding to melting point of pure drug, counteracting the results obtained from FTIR. Absence of stretching vibration of this result might be due to matrix forming effect of hydrogenated soybean castor oil and other polymers with drug.

Particle size distribution, surface morphology and drug content: Particle size study revealed that more than 80% pellets were fall between size ranges of 420-1000µ Table 2. SEM study showed that optimized batch F10 produced smooth, spherical and uniform particle size with more than 90% pellets of 950 µ in diameter as shown in Figure 4. Drug content analysis for all the batches were found to show higher content uniformity with 98% of drug content.

In vitro drug release: Batch1, Ethocel® 7 cps was used as release retardant polymer. The powder blend was granulated with a hydro alcoholic mixture (purified water: isopropyl alcohol – 70:30) since the hydrophobic nature of ethyl cellulose did not allow the use of water as a granulating medium. This formulation was found to show initial burst release Figure 5. In case of batch F2-F4, pellets were comprised of Compritol® 888 ATO and Precirol® ATO 5 as the release retardant matrix. These gave pellets with a rough and irregular surface and could not sustain the drug release. Batch F5, Comprised of Capmul® this was also showing initial burst release. Further batches F6 and F7, were taken using combination of polymer Precirol® ATO 5 and Methocel® K100M, Compritol® 888 ATO and Sterotex® K respectively but these combination also were not helpful to retard the drug release as shown in Figure 6.

For batch F8 –F10, trials were taken with Methocel® K4M and Polyox® WSR303 in addition to lipidic material. Among these formulations, F10 was found to be the most optimized as it provided *Invitro* drug release profile similar to marketed formulation as depicted in Figure 7.

Thus combination of Sterotex® K, Methocel® K4M and Polyox® WSR 303 was optimized for the preparation of extended release pellets formulation of Venlafaxine hydrochloride.

Polyox® WSR 303 has property to prevent initial burst release whereas Sterotex® K and Methocel® K4M were able to retard the subsequent drug release. The calculated similarity factor (F2) value was found to be 56.77, indicating that optimized formulation

showing similar drug release behavior with respect to marketed formulation.

Mathematical modeling fitting: The n (diffusion exponent) and r^2 values for zero-order, first-order, Higuchi and Peppas, and Hixson Crowell models are given in Table 3. The kinetic model that best fitted the *invitro* release data was selected based on the correlation coefficient value (r^2) obtained from various kinetic equations. *Invitro* drug release profiles from all the formulations could be best expressed by Higuchi equation as plot showed highest linearity with r^2 value between 0.980-0.990. Thus it was suggested that drug release from optimized batch took place by diffusion mechanism.

Stability Study: The optimized batch (F10) kept for stability study was showing good drug content uniformity with 99.1±0.5% venlafaxine hydrochloride. *Invitro* drug release profile as shown Figure 8 was found to be similar to marketed formulation and F2 value was found to be 55.35.

CONCLUSION

Venlafaxine hydrochloride extended release matrix pellets was successfully formulated with Sterotex® K, HPMC K 4M and Polyox WSR ®303 as matrix former polymer. *Invitro* release kinetic study indicated that drug releases by diffusion mechanism form the optimized formulation. Developed extended release pellets formulation is expected to reduce the administering frequency and dose dumping effect with reduction in adverse effect associated with frequent administration of Venlafaxine HCl tablets.

ACKNOWLEDGMENT

UGC for fellowship, Amoli Organics Pvt. Ltd. for gift sample of Venlafaxine Hydrochloride, Gattffosse for gift samples of Compritol® 888ATO and Precirol® ATO 5, Abitec group for Sterotex® K and Capmul® gift samples, Colorcon Asia Pvt. Ltd. for gift sample of Methocel®, Dow chemical corporation for Polyox® WSR303, Signet chemical Corporation for Avicel® PH101 .

Figure 1: Parts of a Single Screw Extruder (Manual – Axial type

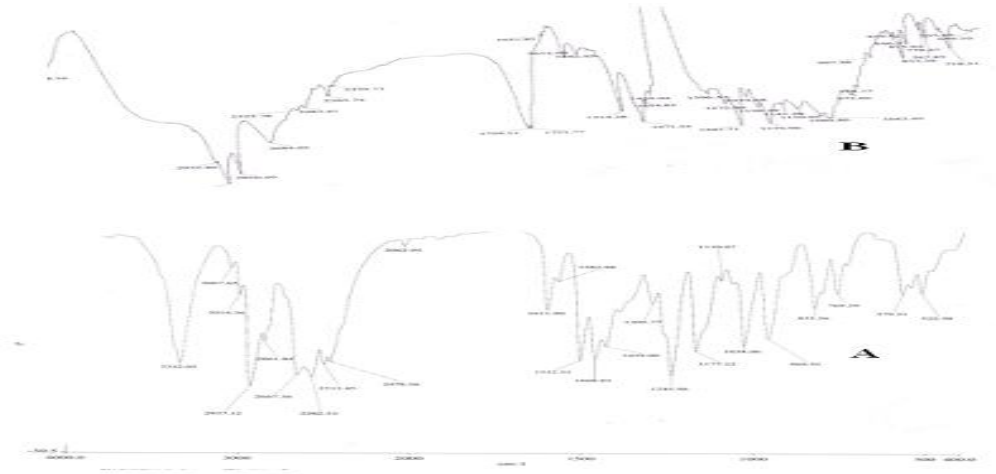

Figure 2: FTIR spectra of (A) Pure Venlafaxine Hydrochloride and (B) Venlafaxine pellets formulation

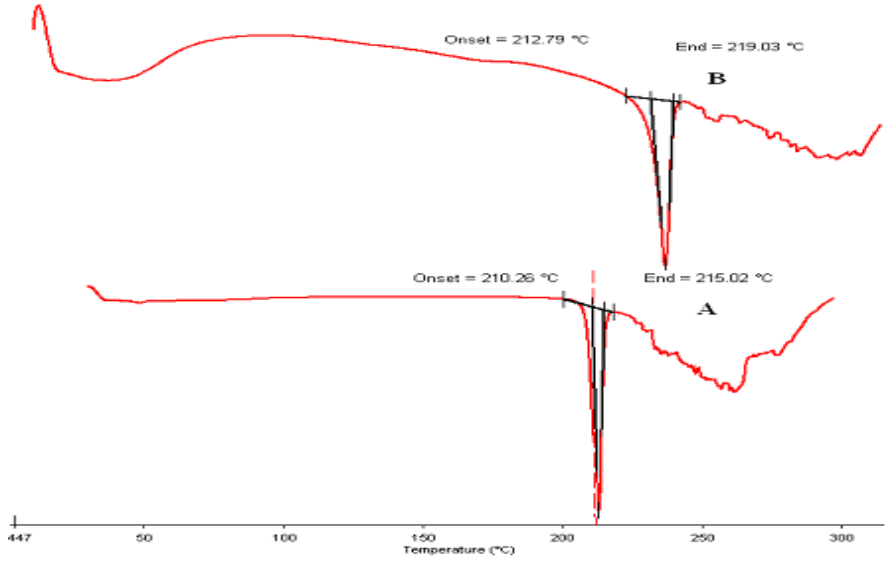

Figure 3: DSC thermogram of (A) Pure Venlafaxine Hydrochloride and (B) Venlafaxine pellets formulation

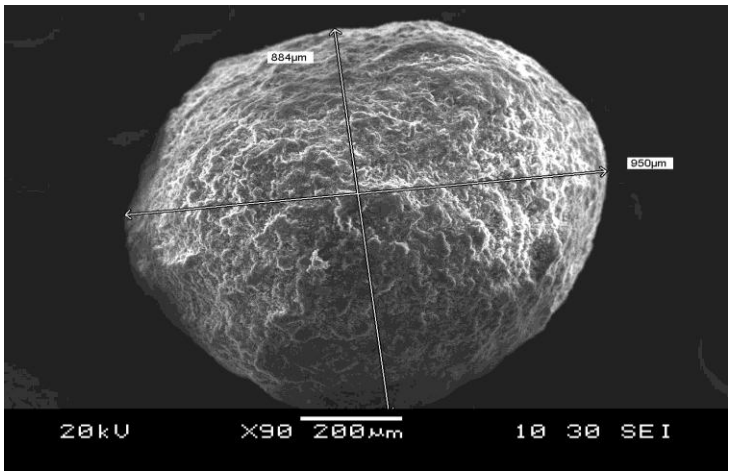

Figure 4: SEM of Venlafaxine hydrochloride pellets

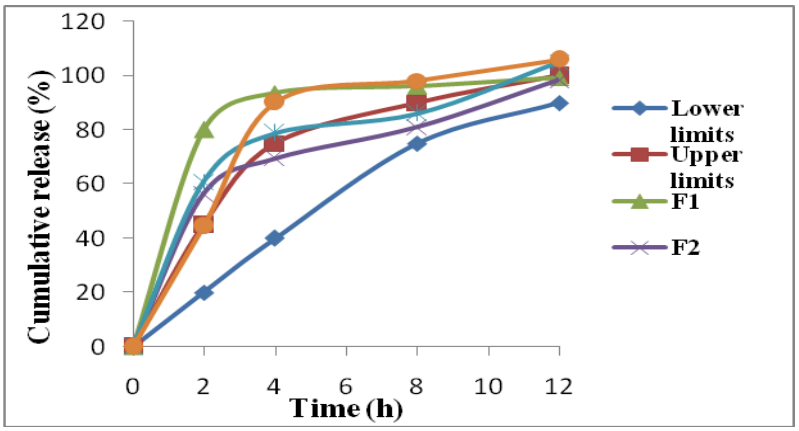

Figure 5: *Invitro* drug release profiles for batch F1-F4

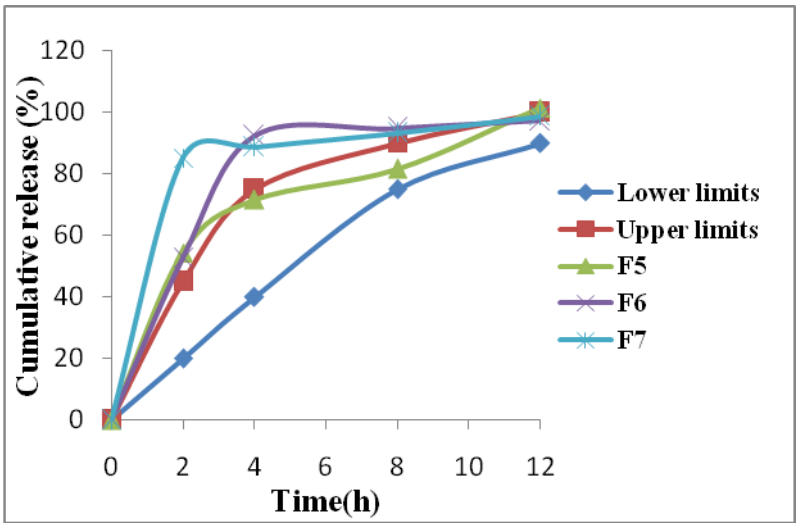

Figure 6: *Invitro* drug release profiles for batch F5-F7

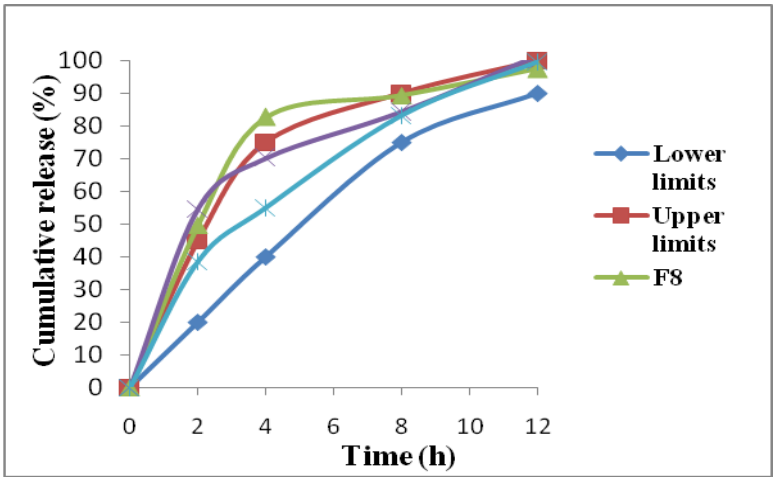

Figure 7: *Invitro* drug release profiles for batch F7-F10

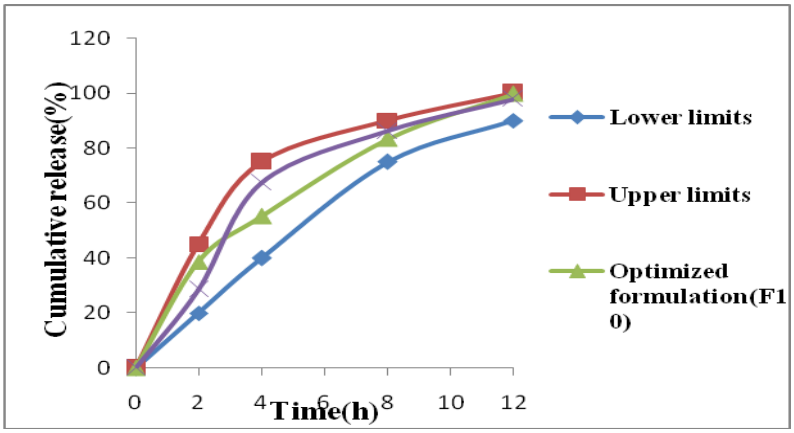

Figure 8: *Invitro* drug release profile of stability batch

Table 1: Formulation compositions for different pellets batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Venlafaxine HCl	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
Ethocel® 7cp	62.5	-	-	-	-	-	-		-	-
Compritol® 888 ATO	-	62.5	25	-		-	37.5	50	-	-
Precirol® ATO 5	-	-	-	62.5	-	50	-	-	-	-
Sterotex® K	-	-	-	-	-	-	25	12.5	50	37.5
Methocel® K15M	-	-	37.5	-	-	-	-	-	-	--
Capmul®	-	-	-	-	62.5	-	-	-	-	-
Methocle® K100M	-	-	-	-	-	12.5	-	-	-	-
Methocle® K4M	-	-	-	-	-	-	-	-	12.5	12.5
Polyox® WSR 303	-	-	-	-	-	-	-	-	-	12.5
PEG	-	-	-	-	-	-	2.5	-	-	-
Avicel PH 101	25	25	25	25	25	25	22.5	25	25	25
Total (mg)	125	125	125	125	125	125	125	125	125	125

Table 2: Physical parameters characterizations

Batch No	Particle size (420-1000µ) in %	Observations	Drug content (%)
F1	70	irregular surface and dumbbell shape pellets	98.21±1.34
F2	90	Smooth, uniform in size and shape pellets	98.21±2.20
F3	75	elongated rod like structures	98.61±0.84
F4	80	irregular surface and shape, coarse aggregate formed	100.25±2.23
F5	85	spherical pellets but size was not uniform size	98.01±1.04
F6	90	spherical pellets	98.26±2.04
F7	75	dumbbell shape pellets	98.31±2.24
F8	80	irregular surface and dumbbell in shape	99.21±1.12
F9	85	spherical pellets with irregular surface	101.11±2.14
F10	90	smooth, spherical and uniform size pellets	99.93±3.094

Table 3: *Invitro* release kinetic parameters

Batches	Zero order		First order		Higuchi		Hixon-Crowell		Korsmeyer-Peppas		
	r^2	K	r^2	k	r^2	K	r^2	k	n	r^2	K
F1	0.714	41.52	0.965	1.705	0.891	19.59	0884	-1.582	0.431	0.986	1.192
F2	0.875	25.70	-0.953	2.02	0.977	7.92	0.970	-0.746	2.320	0.987	0.551
F3	0.857	28.98	-0.961	1.99	0.960	10.797	0.963	-1.053	1.64	0.003	0.641
F4	0.836	27.24	-0.986	1.96	0.947	6.71	0.940	-0.609	0.189	0.889	2.76
F5	0.881	25.22	-0.932	2.10	0.980	7.286	0.970	-0.442	2.22	0.990	0.598
F6	0.802	31.12	-0.924	1.80	0.935	10.46	0.882	-0.798	0.553	0.975	1.44
F7	0.696	42.18	-0.941	1.71	0.876	20.735	0.859	-1.623	0.791	0.981	0.488
F8	0.848	27.16	-0.983	1.92	0.963	7.88	0.953	-1.03	1.245	0.986	1.121
F9	0.886	25.02	-0.944	2.10	0.983	7.03	0.970	-0.522	1.88	0.975	0.991
F10	0.960	14.91	-0.933	2.23	0.990	-1.24	0.988	0.324	1.855	0.932	1.821

REFERENCES

1. Ghebre-Sellassie. Pellets: A general overview. In: I. Ghebre-Sellassie (eds). Pharmaceutical Pelletization Technology, New York and Basel; Marcel Dekker Inc.; 1989, pp.1–13

2. Bechgaard H, Hagermann NG. Drug Dev Ind Pharm, 1978; 4: 53–67.
3. Berner B, Dinh S. Fundamental concepts in controlled release. In: Treatise on Controlled Drug Delivery (Kydoneus, A., eds.), New York; Marcel Dekker Inc: 1992.
4. Marijima T, McGinity JB. Pharm Dev Tech, 2000; 116: 211-221.
5. Muth EA, Haskins JT, Moyer JA, Husbands GE, Nielson ST, Sigg EB. Biochem Pharmacol, 1986; 35(24): 4493–4497.
6. Madgulkar AR, Bhalekar MR, Kolhe VJ, Kenjale YD. Indian J Pharm Sci, 2009; 71(4): 387-394.
7. Chen AX, Kigin PD. US patent, US 20080220079, 1996.
8. Sheman DM, Clark JC, Lamer JU, White SA. US Patent, US 6403120, 2002.
9. Doshi CC, Gopinathan D, Kulkarni S, Sukthankar M, Thakker P. US Patent, US 20060115526A1, 2004.
10. Dixit M, Cheng XX, Nangia A, Chen CM. US Patent, US 20110165234, 2011.
11. Madat DV, Gohel MC. J Pharm Res, 2011; 4(3): 607-609.
12. Tian L. et al, Sustained-release pellets prepared by combination of wax matrices and double-layer coatings for extremely water-soluble drugs, Drug Dev Ind Pharm 2008; 34(6): 569- 576.
13. Hadjiioannou TP, Christian GD, Koupparis MA, Macheras PE. Quantitative calculations in pharmaceutical practice and research, New York; VCH Publishers Inc.; 1993, pp. 345-348.
14. Bourne DWA. Pharmacokinetics. In: Banker GS, Rhodes CT, Modern Pharmaceutics, (4th ed.), New York; Marcel Dekker Inc: 2002, pp.67-92.
15. Higuchi T. J Pharm Sci, 1963; 52(12): 1145-1149.
16. Hixson AW, Crowell JH. Ind Eng Chem, 1931; 23: 923-931.
17. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas. Int J Pharm, 1983; 15:25-35.