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Research Article

FORMULATION, OPTIMISATION AND IN VITRO EVALUATION OF MOUTH DISSOLVING TABLETS OF VENLAFAXINE HYDROCHLORIDE

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ABSTRACT

Objective: The purpose of the present investigation is to formulate, optimize, evaluate and comparative study of mouth dissolving tablets of Venlafaxine Hydrochloride, a novel antidepressant by direct compression method, which is simple and cost effective.

Methods: Eighteen formulations, F1-F18 were formulated by using different concentrations of superdisintegrants i.e.,Crospovidone, Croscarmellose sodium and Sodium starch glycolate as 1-6% w/w.The prepared tablets were evaluated for micromeritic properties, hardness, friability, weight variation, wetting time, water absorption ratio, *in-vitro* disintegration, *in-vitro* dispersion time and *in-vitro* drug release.

Results: The drug-excipient interactions were investigated by FTIR and it was found that there was no interaction between drug and Excipients. The micromeritic properties, hardness, friability, weight variation and drug content of all the formulations were within the acceptable limits of the British Pharmacopoeia. Amongst eighteen promising formulations, the best formulation, F12 (6% Croscarmellose sodium) provided short wetting time of 47sec, water absorption ratio of 100%, *In-vitro* dispersion time of 34sec and *in vitro* disintegration of 15 seconds. This optimized formulation showed good release profile with complete drug release i.e.99.59% within 2min is compared with control tablet without super disintegrating agent. The data of the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of Venlafaxine Hydrochloride from mouth dissolving tablets. Hence the drug release followed the first order release kinetics and Peppas model indicates the mechanism of drug release was Non–Fickian diffusion.

Conclusion: It was concluded that mouth dissolving tablets of Venlafaxine Hydrochloride can be successfully formulated by superdisintegrant addition method with improved patient compliance.

Keywords: Venlafaxine Hydrochloride, Mouth dissolving tablets, I*n-vitro* dispersion time, Wetting time, Direct compression.

INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance [1]. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow [2]. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis [3].

In certain people, the use of conventional tablets can give trouble, such as the elderly (geriatric) who are experiencing difficulties in using conventional dosage forms (solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia; and children (pediatric) who have problems in swallowing drugs because of muscular and nervous system has not fully developed. Also in patients who have trouble using conventional tablets, such as in mentally ill patients, patients who are paralyzed, patients who are unable to swallow and patients who have to avoid much water, as well as in people who experience nausea [4,5,6]. MDT is not only indicated for people who have swallowing difficulties, but also are ideal for active working or travelling people [7, 8]. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.

In mammals the ingestive response to sweeteners, amino acids and many bitter compounds is initiated by the interaction of chemical compounds with G–protein coupled receptor (GPCRs) on the apical membrane of taste cell. Two families of GPCR are known to mediate this detection process- the T2Rs and T1Rs. T2Rs –respond selectively to compounds that elicit bitter taste sensation in humans.T1Rs which appear to function predominantly as heterodimers are activated by amino acids and sweetener (artificial and natural)[9,10]

Mouth dissolving tablets are solid dosage form that disintegrates and dissolves in mouth without water within 60 seconds or less [11] and are also called as fast-dissolving tablets, melt-in mouth tablets, oro-dispersible tablets, rapimelts, porous tablets, quick dissolving etc. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach [12]. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.

The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics [13]. The basic approach in development of MDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), crospovidone etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pre-gastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet.

Venlafaxine HCl is a representative of new class of antidepressants. It acts by inhibiting selectively the uptake of serotonin and nor -adrenaline but shows no affinity for neurotransmitter receptors. Hence it lacks the adverse anti-cholinergic, sedative and cardiovascular effects of tricyclic antidepressants. However the main limitation to therapeutic effectiveness of venlafaxine HCl is its poor bioavailability (40-45%) and short half life (5 hrs) necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug. These products are indicated for the treatment of depressive illness including depression accompanied by anxiety. Following an initial response Venlafaxine is indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes. Venlafaxine tablets contain the active ingredient Venlafaxine, as Venlafaxine hydrochloride [14].

Selected drug Venlafaxine hydrochloride is not available as mouth dissolving formulation in market. This type of formulation play very important factor for the patients, who really in need of this type of the formulation. Especially these formulations are designed with using sweetening agents (sodium saccharin) and flavors (peppermint oil) which still make more compliance with taste and smell. Usually the mouth dissolving tablets are formulated by various techniques like freeze drying technique, Durasolv technique [15], etc. In the recent past, several new advanced technologies have been introduced for the formulation of (ODTs) like lyophilization [16], moulding [17], direct compression [18], cotton candy process [19], spray drying [20], sublimation [21], mass extrusion [22], nanonization [23] and quick dissolve film formation [24]. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets [25].

Hence, the design of the formulation of Mouth Dissolving Tablets of Venlafaxine Hydrochloride is majorly focused on direct compression which is cost effective, when compared to other technologies.

MATERIALS AND METHODS

Materials

Venlafaxine Hydrochloride was obtained as gift sample from Emco Industries, Hyderabad, India, Sodium starch glycolate ,Crospovidone , Croscarmellose sodium were obtained from Amit Cellulose Products. Pune . Microcrystalline cellulose pH102 was obtained from Wei Ming Pharmaceutical Mfg. Co. Ltd, Taiwan. All other chemicals and solvents used were of analytical grade.

Methods

Preparation of Mouth dissolving tablets of Venlafaxine Hydrochloride by direct compression method

The direct compression technique was used to manufacture the tablets. The drug and the excipients were passed through #60-sieve. Weighed amount of drug and excipients except magnesium stearate were mixed by geometric addition method for 20 minutes manually. The blend was then lubricated by further mixing with magnesium stearate (#60-sieve). All the above ingredients were subjected for drying to remove the moisture content at 40 to 45oC, the mixture was blended with flavor and the powder blend was then compressed on double station rotary punching machine using flat faced punches. Round punches measuring 8 mm diameter were used for compression of tablets. The composition of formulations shown in Table 1 & 2.

Drug-Excipient compatibility studies

The drug polymer and polymer-polymer interaction was studied by the FTIR spectrometer using Shimadzu 8400-S, Japan. Two percent (w/w) of the sample with respect to a potassium bromide disc was mixed with dry KBr. The mixture was grind into a fine powder using an agate mortar and then compressed into a KBr disc in a hydraulic press at a pressure of 1000psi. Each KBr disc was scanned 16 times at 2 mm/sec at a resolution of 4 cm-1 using cosine apodization. The characteristic peaks were recorded.

Table 1: Formulation of Venlafaxine Hydrochloride Mouth dissolving tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Drug	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
Cros povidone	2	4	6	8	10	12	-	-	-	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	2	4	6	8	10	12	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	-	2	4	6	8	10	12
Microcrystalline cellulose	20	40	70	80	90	100	20	40	70	80	90	100	20	40	70	80	90	100
Mannitol	125.5	103.5	71.5	59.5	47.5	35.5	125.5	103.5	71.5	59.5	47.5	35.5	125.5	103.5	71.5	59.5	47.5	35.5
Sodium saccharine	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Flavors	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total wt.(mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Formulation of control tablet: (F12 without using superdisintegrant)

Name of ingredients	Quantity (in mg)
Venlafaxine hydrochloride	37.5
Mannitol	47.5
MCC	100
Sod. Saccharin	10
Flavor	2
Magnesium stearate	3
Talc	2
Total	200

Evaluation of Venlafaxine Hydrochloride Mouth Dissolving Tablets

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. pre compression parameters (Angle of repose, Bulk density, Tapped density, Compressibility index, Hausner's ratio) and post compression parameters (Weight uniformity test, Hardness, Friability, Drug content uniformity , water absorption ratio, wetting time, *In-vitro* disintegration time, *In-vitro* dispersion time and *In - vitro* drug release).

Pre-compression studies [26-29]

The evaluations of Pre-compression studies of formulated mouth dissolving tablets of Venlafaxine Hydrochloride were done as per standard procedures. The following parameters were evaluated.

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve #20) in to a measuring cylinder and the initial volume was noted, it is bulk volume. The bulk density is calculated by given formula,

Bulk density (ρ_b) = Mass of the powder (M) / Bulk volume (V_B)

Tapped density

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times.. It is expressed by given formula,

Tapped density (ρ_T) = Mass of the powder (M) / Tapped volume (V_T)

Carr's Index

It is the simple test to evaluate the bulk density and tapped density of a powder and the rate at which it packed down. It is expressed by the given formula,

Carr's Index (%) = [(Tapped density – Bulk density)×100] / tapped density

Hausner's Ratio: It is the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density / Bulk density

Angle of repose

Angle of repose of powdered blend was determined by the funnel method. The accurately powdered blends were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powdered blend was allowed to through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated by using the following formula,

$$\tan \emptyset = h/r$$

h = height of the powder cone, Ø= angle of repose

r = radius of the powder cone

Post- compression studies

Thickness [30]

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier caliper (Pico India). The average values were calculated.

Hardness Test [31,32]

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets.

The hardness was tested using Monsanto tester. "Hardness factor", the average of the four determinations, was determined and reported. The force was measured in kilograms per centimeter square.

Friability Test [31,32]

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1.0 %. Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. The percent friability was determined using the following formula;

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

Where, W1 = weight of the tablet before test, W2 = weight of the tablets after test.

Weight Uniformity Test [31,32]

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percent deviation was calculated using the following formula.

$$\text{Percentage Deviation} = \frac{\text{Individual weight - Average weight}}{\text{Average weight}} \times 100$$

Any variation in the weight of tablet (for any reason) leads to either under medication or over medication. So, every tablet in each batch should have a uniform weight. Deviation within the IP permissible limit of 7.5% is allowed as the tablet weighs 200 mg. Corrections were made during the compression of tablets to get uniform weight.

Content Uniformity Test [31,32]

Three tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablet powder was taken from the crushed blend. Then the samples were transferred to three 100 ml volumetric flasks and were diluted up to the mark with phosphate buffer (pH 6.8) solution. The contents were shaken periodically and kept for 24 hours for solvation of drug completely. The mixtures were filtered, appropriately diluted, and absorbances were measured at λmax 274 nm against blank reference. The drug content in each tablet was calculated.

***In- vitro* Disintegration Time [33]**

In-vitro Disintegration times for mouth dissolving tablets were determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 as medium. The volume of medium was 900 ml and temp was 37± .5 °C. The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

***In -vitro* Dispersion Time [34]**

In -vitro dispersion time was measured by dropping a tablet into a Petri dish containing 10 ml of phosphate buffer solution, pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and tested. *In-vitro* dispersion time was found and expressed in seconds.

Wetting Time [35]

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablets is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablet can be measured using a simple procedure.

Two circular tissue papers of 10 cm diameter are placed in a Petri dish having the same inner diameter. Ten ml of phosphate buffer solution, 6.8 pH is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper so that complete tablet was not immersed in the solution. Then, the time required for buffer to reach upper surface of the tablet is noted as wetting time.

Water absorption ratio [35]

A piece of tissue paper folded twice was placed in a small Petri dish Containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted.

Water absorption ratio, R was determined using following equation.

R = 100 × Wa –Wb/Wa

Where, Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption

***In-vitro* Drug Release**

In-vitro drug release of the samples was carried out using USP - type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of phosphate buffer (pH 6.8) solution, was placed into the dissolution flask maintaining the temperature of 37±0.5oC and rpm of 50. One Venlafaxine Hydrochloride tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 30min. Samples measuring 5 ml were withdrawn after every 1, 2, 3, 4, 5 and 10 min interval. Samples were filtered through whatman filter paper no: 40.The fresh dissolution medium was replaced every time with the same quantity of the sample. The collected samples were analyzed at 274 nm using dissolution medium as blank. The cumulative percentage drug release was calculated.

Drug release kinetics

To examine the release mechanism of Venlafaxine Hydrochloride from the prepared mouth dissolving tablets, the results were analyzed according to the following equation:

$$\frac{M_t}{M} = k.t^n$$

Where M_t / M is the fractional drug released at time t, k is a kinetic constant incorporating structural and geometrical characteristics of the drug/polymer system and n is the diffusional exponent that characterizes the mechanism of drug release. It is known that for non-swelling tablets, the drug release can generally be expressed by the Fickian diffusion mechanism, for which n = 0.5, whereas for most erodible matrices, a zero-order release rate kinetics is followed, for which n = 1. For non-Fickian release, the n value falls between 0.5 and 1.0 [0.5 < n < 1.0]; whereas in the case super case II transport n > 1.

The data of the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of Venlafaxine Hydrochloride from mouth dissolving tablets. The kinetic models used were Zero-order equation [36] (eq. 1), First-order equation [37] (eq. 2), Higuchi equation [38] (eq. 3) and Korsmeyer-Peppas equation [39] (eq. 4).

$Q_t = K_0 t$ ---------- (1)

$Q_t = Q_0 (1- e^{-k1}t)$ ---------- (2)

$Q_t = K_H.t^{1/2}$---------- (3)

$Q_t / Q_\infty = K_k t^n$---------- (4)

Where,

Q_t ------- Is the amount of drug release in time t

Q_0 ------- Is the initial amount of the drug

n ------- Exponent value

And K_0, K_1, K_H, and K_k are release rate constants for Zero-order, First-order, Higuchi, and Krosmeyer-Peppas model respectively.

Data of the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of Venlafaxine Hydrochloride from mouth dissolving tablets.

RESULTS AND DISCUSSION

Drug-Excipients compatibility study

The IR spectrum of Venlafaxine Hydrochloride and other excipients were determined and it was found that there were no any extra peaks observed, which indicating that there was no interaction between drug and excipients. The results are shown in Figures 1 - 5.

Preformulation studies

In the Preformulation studies, blended powered drug were conducted for the Angle of repose, Bulk density, Tapped density, Carr's index and Hausners ratio. From the results it is indicated that the angle of repose was low, good compressibility and found "good" to "excellent" flowability. The porosity gets altered by the number of contact points and by the shape and diameter of constituent particles. As tablet porosity and average pore size decreases with increase in compression force due to high compressibility of microcrystalline cellulose, it was observed that there is decrease in porosity with increase in microcrystalline cellulose contents. The results are shown in Table 3.

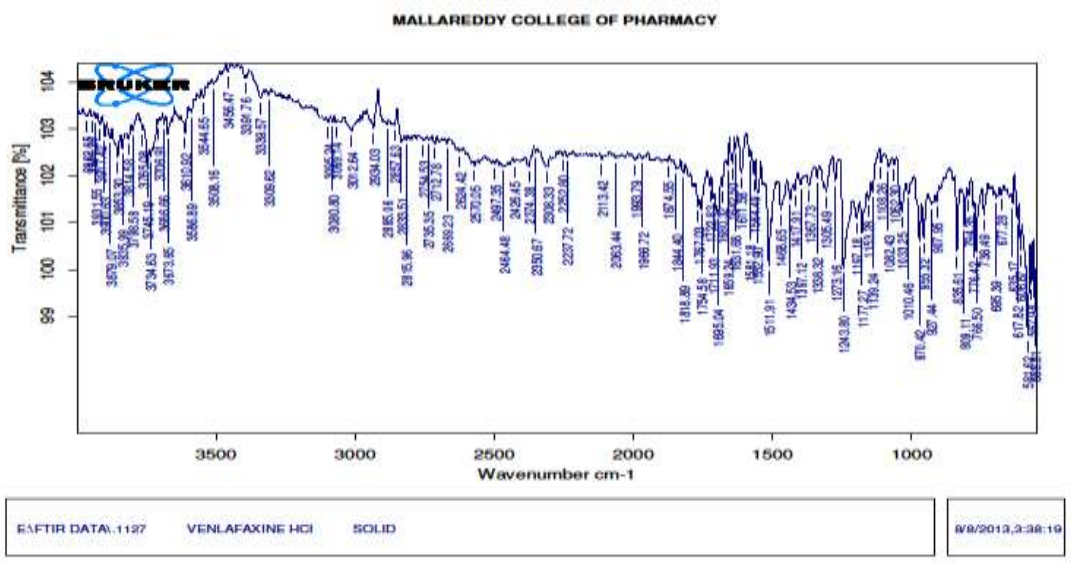

Fig. 1: FTIR Spectrum of Venlafaxine Hydrochloride.

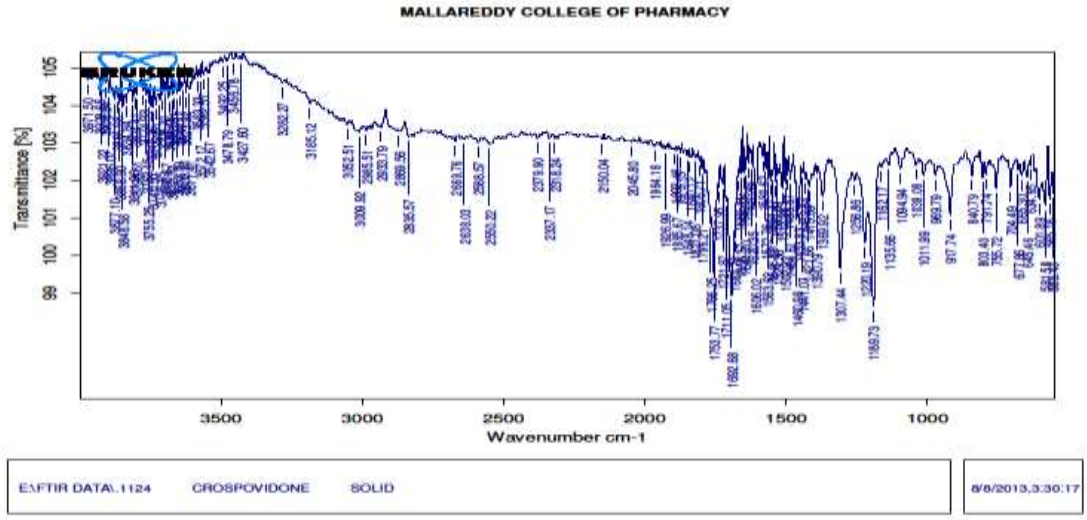

Fig. 2: FTIR Spectrum of Crospovidone.

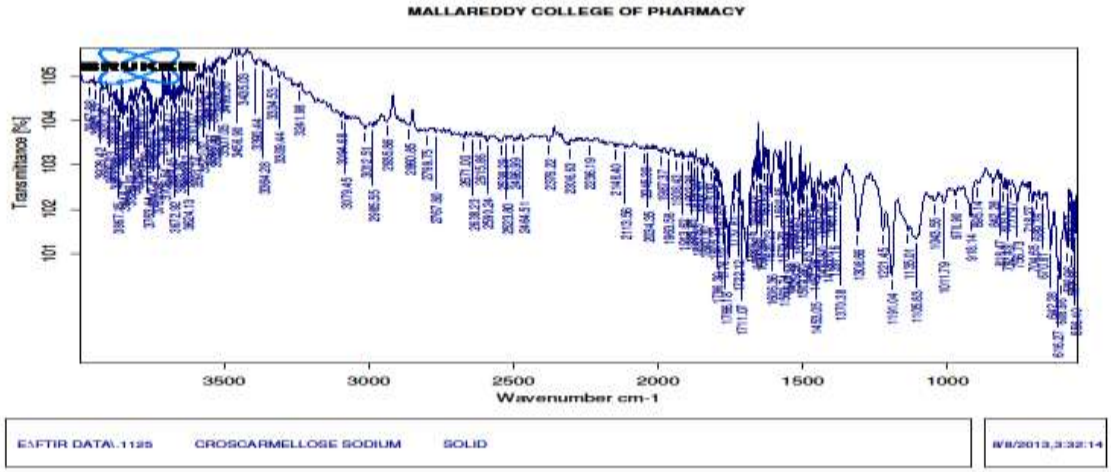

Fig. 3: FTIR Spectrum of Croscarmellose sodium.

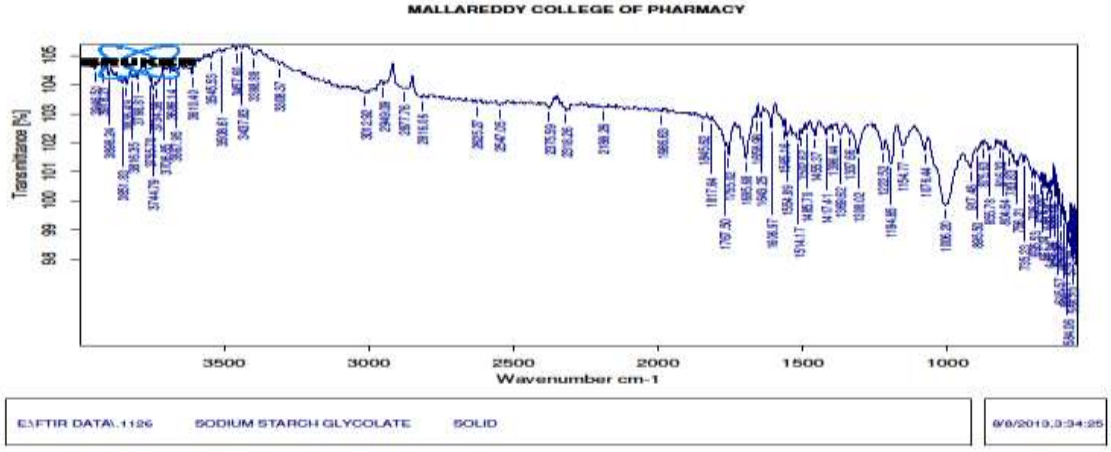

Fig. 4: FTIR Spectrum of Sodium starch glycolate.

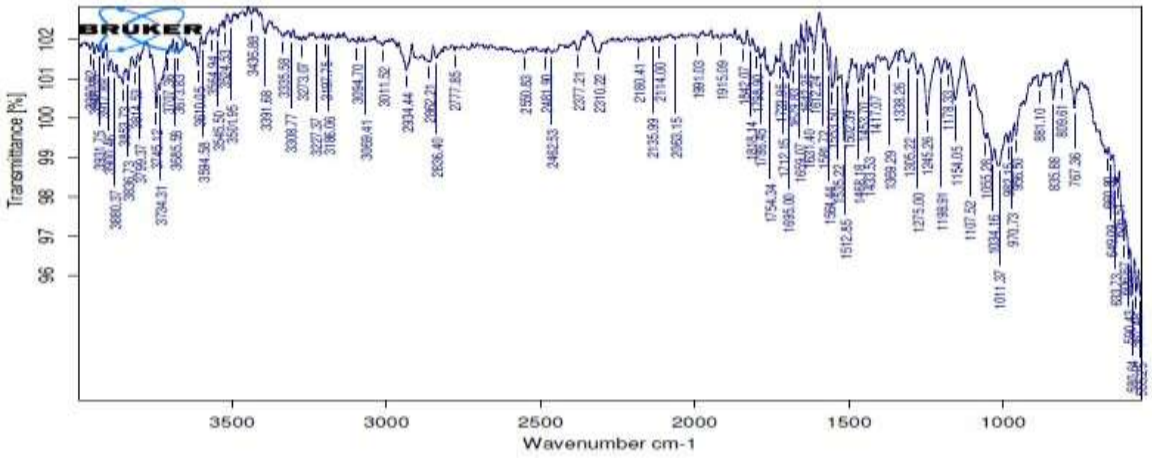

Fig. 5: FTIR Spectrum of successful formulation F12.

Table 3: Pre-compression studies for formulations F1-F18 and F12 CT

Formulation code	Angle of repose(degree) ± *SD	Bulk density(gm/cc)± *SD	Tapped density(gm/cc)± *SD	Carr's index (%)± *SD	Hausner ratio± *SD
F1	27.96±1.56	0.588±0.007	0.714±0.01	17.64±1	1.21±0.03
F2	28.50±1.20	0.625±0.007	0.769±0.01	18.72±1.51	1.23±0.04
F3	29.03±1.70	0.625±0.007	0.714±0.02	12.46±1.20	1.14±0.03
F4	26.1±0.88	0.625±0.007	0.714±0.01	12.46±2.51	1.14±0.03
F5	26.1±1.48	0.588±0.007	0.714±0.01	17.64±1.58	1.21±0.03
F6	24.79±1.22	0.625±0.007	0.714±0.02	12.46±1.55	1.14±0.04
F7	27.47±1.32	0.625±0.007	0.769±0.38	18.72±1.39	1.23±0.04
F8	29.03±1.34	0.588±0.007	0.714±0.02	17.64±2.20	1.21±0.03
F9	29.59±1.26	0.625±0.007	0.714±0.01	12.46±2.01	1.14±0.03
F10	25.64±1.20	0.625±0.007	0.714±0.01	12.46±2.12	1.14±0.04
F11	25.22±1.26	0.625±0.007	0.714±0.02	12.46±1.51	1.14±0.03
F12	25.24±1.20	0.625±0.007	0.714±0.01	12.46±1.39	1.14±0.03
F13	31.34±1.56	0.666±0.007	0.769±0.02	13.39±1.20	1.15±0.04
F14	28.50±1.41	0.666±0.007	0.769±0.01	13.39±1.67	1.15±0.02
F15	27.47±1.33	0.625±0.007	0.769±0.02	18.72±1.41	1.23±0.03
F16	25.22±1.67	0.666±0.007	0.769±0.02	13.39±2.51	1.15±0.03
F17	26.1±1.33	0.625±0.007	0.714±0.01	12.46±1.41	1.14±0.02
F18	26.1±1.41	0.666±0.007	0.769±0.01	13.39±1.67	1.15±0.02
F12 CT	27.47±1.22	0.588±0.007	0.714±0.01	12.46±1.20	1.22±0.04

n=3, ±S.D.

Evaluation of Mouth Dissolving Tablets of Venlafaxine Hydrochloride

Hardness and Friability

Tablets required certain amount of strength or hardness and resistance to friability. It is necessary or important to withstand mechanical shocks of handling in manufacture, packaging and shipping. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. Using tablets hardness tester, hardness of the tablets were checked.

The results are shown in Table 4. From the above studies it was found that hardness and friability are within the pharmacopeias limits.

Thickness

The Thickness of tablets was found to be between 4.5±0.03mm to 4.9±0.01 mm but the thickness of tablets prepared without superdisintegrant means control tablet had thickness of 4.9±0.09mm. The results are shown in Table 4.

Weight variation

The Weight variation was found within the pharmacopoeial limits. The results are shown in Table 4.

Drug content uniformity

The results indicated that the content of Venlafaxine Hydrochloride in all the formulations i.e. F1 to F18 were found to be in the range of 98 to 103% which are within the Pharmacopeial limits. The results are shown in Table 5.

Wetting time and Water absorption ratio

The wetting time and water absorption ratio which are the important criteria for determining the capacity of disintegrates to swell in presence of little water or saliva.

The best result has been shown by formulation, F12 tablets, it showed the water absorption ratio and wetting time was 100.5**±**0.40 % and 47**±**0.34 seconds. Thus the results indicated that the preparation was more water absorption ratio and minimum wetting time, so it will take less time for disintegrating. The results are shown in Table 5 and Fig.6-7.

***In- vitro* disintegration time**

The disintegration time of mouth dissolving tablets should be less because in a very short time it should be totally disintegrates. The disintegration time for control tablet was 129 sec., which was very high. This was due to no superdisintegrant was used. The

superdisintegrants were used in tablets which shown the better result. Among the F1 to F18 formulations and F12CT, the best formulation, F12 was found to be minimum *in-vitro* disintegration time of 15 sec. Because, with increase in concentration of superdisintegrant, disintegration time decreases. The results are shown in Table 5 and Fig.8.

***In-vitro* dispersion time**

The dispersion in mouth is a very important consideration during the formulation of mouth dissolving tablets. Among the F1 to F18 formulations and F12CT, the best formulation, F12 was found to be minimum *in-vitro* dispersion time of 34**±**1.32 sec. The results are shown in Table 5 and Fig. 9.

***In-vitro* dissolution study**

Dissolution rate studies showed that about complete drug release occurred within 1 to 15 minutes for all formulations with using the superdisintegrant but in case for control tablet showed complete release of drug i.e. 99% in 10 minutes without use of superdisintegrant. The results are shown in Fig10-12.The results indicate that the formulation, F12 which was prepared by the superdisintegrant croscarmellose with 6% showed the complete drug released i.e. 99.59% within 2 minutes. Thus, there was an indication that the formulation F12 has better result on comparison to others formulations. Comparison of dissolution profile was conducted with best formulation, F12 and control tablet F12CT. The results are shown in Fig 13.

Drug release kinetic studies

The I*n-vitro* drug release data of all Venlafaxine Hydrochloride mouth dissolving tablets were subjected to goodness of fit test by linear regression analysis according to Zero order equation, 1st order equation, Higuchi's equation and Krosmeyer-Peppas equation to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficient are presented in Table7.Among the regression correlation co-efficient (R^2) values of first order equation was found to be higher, similarly among the Higuchi's equation and Krosmeyer-Peppas equation, the (R^2) values of Krosmeyer-Peppas equation was found to be higher. Hence the drug release followed the first order release kinetics and Peppas model indicates the mechanism of drug release i.e., Non-Fickian diffusion.

Table 4: Weight variation, Hardness, Thickness and Friability for formulations F1-F18 and F12 CT

Formulation code	Weight variation(mg) ± *SD	Hardness (kg/ cm²) ± *SD	Thickness (mm) ± *SD	Friability (%)
F1	197.5±1.15	2.3±0.04	4.6±0.07	0.39
F2	203.1±1.38	2.4±0.12	4.8±0.01	0.25
F3	205.7±0.74	2.4±0.05	4.7±0.02	0.62
F4	197.3±1.14	2.5±0.08	4.8±0.05	0.37
F5	207.6±0.85	2.3±0.06	4.9±0.03	0.63
F6	201.4±1.01	2.3±0.03	4.9±0.01	0.25
F7	195.1±0.52	2.4±0.07	4.7±0.06	0.37
F8	198.2±0.34	2.4±0.06	4.6±0.03	0.25
F9	202.1±0.48	2.9±0.08	4.6±0.05	0.91
F10	200.15±1.83	2.3±0.05	4.5±0.02	0.50
F11	198.7±1.99	2.4±0.16	4.6±0.03	0.25
F12	200.4±1.13	2.5±0.11	4.7±0.03	0.62
F13	199.6±1.16	2.4±0.05	4.7±0.03	0.51
F14	202.2±0.74	2.4±0.14	4.7±0.09	0.99
F15	196.6±0.33	2.6±0.14	4.6±0.06	0.38
F16	198.7±0.14	2.6±0.14	4.6±0.03	0.75
F17	202.4±0.28	2.7±0.06	4.5±0.03	0.76
F18	196.2±0.23	2.9±0.05	4.6±0.08	0.38
F12 CT	202.1±0.48	3.5±0.08	4.9±0.09	0.62

n=3, ±S.D.

Table 5: Drug content Assay, Wetting time, Water absorption ratio, *in-vitro* Disintegration time and *In- vitro* Dispersion Time for formulations F1-F18 and F12 CT

Formulation Code	Wetting time (sec) ± *SD	Water absorption ratio(%)± *SD	*In vitro* Disintegration time (sec)	*In-vitro* Dispersion Time (sec) ± *SD	Drug content Assay (%)
F1	250±0.25	41.29±0.48	116	201±1.12	103
F2	195±0.87	67.15±0.95	88	169±1.54	101
F3	93±0.99	84.34±0.35	68	90±1.25	98
F4	89±1.25	85.19±0.85	55	72±1.08	102
F5	75±1.35	87.2±0.92	29	63±1.04	102
F6	71±1.15	88.2±0.95	24	53±0.89	98
F7	212±0.98	63.63±0.58	114	176±0.54	103
F8	135±0.88	65.21±0.54	70	126±1.14	101
F9	59±0.78	84.91±0.45	52	47±0.68	99
F10	59±0.61	96.83±0.24	42	46±1.14	104
F11	52±0.20	99.51±0.56	31	39±0.36	102
F12	47±0.34	100.5±0.40	15	34±1.32	98
F13	53±0.15	35.28±0.54	62	52±1.16	104
F14	51±0.85	69.21±0.82	56	49±1.34	98
F15	46±0.92	97.36±0.62	47	44±1.34	98
F16	45±0.85	99.15±0.26	43	42±1.45	102
F17	41±0.23	99.05±0.48	35	39±1.24	101
F18	37±0.24	102.25±0.62	29	38±0.98	99
F12 CT	202±0.24	29±0.82	129	153±0.36	98

n=3, ±S.D.

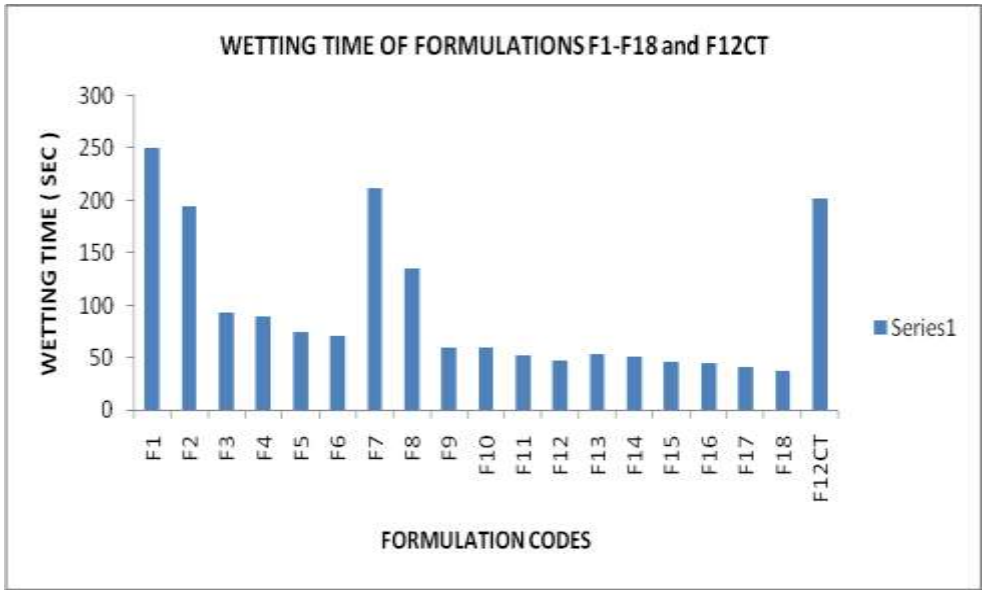

Fig. 6: Wetting Time of Venlafaxine Hydrochloride Formulations F1 to F18 and F12CT

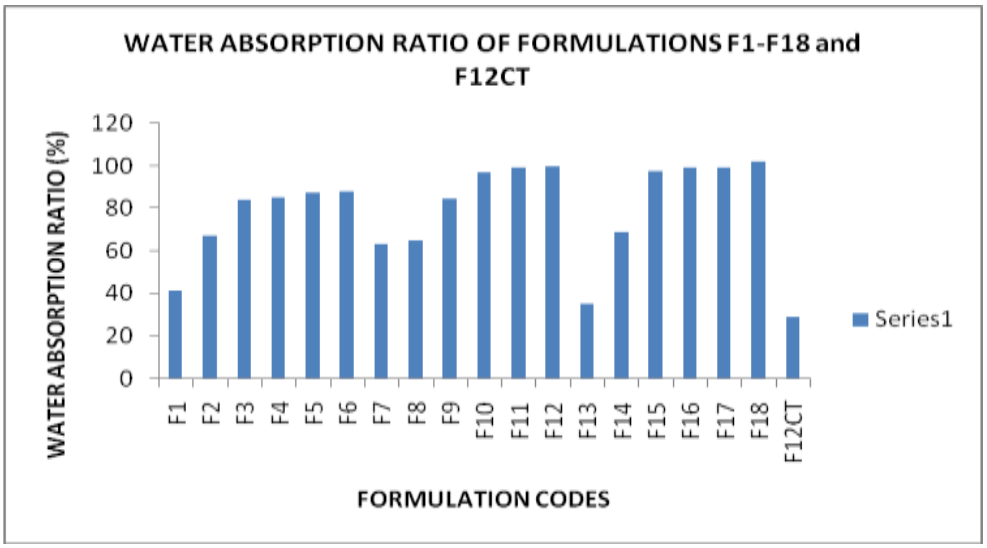

Fig. 7: Water Absorption Ratio of Venlafaxine Hydrochloride Formulations F1 to F18 and F12CT

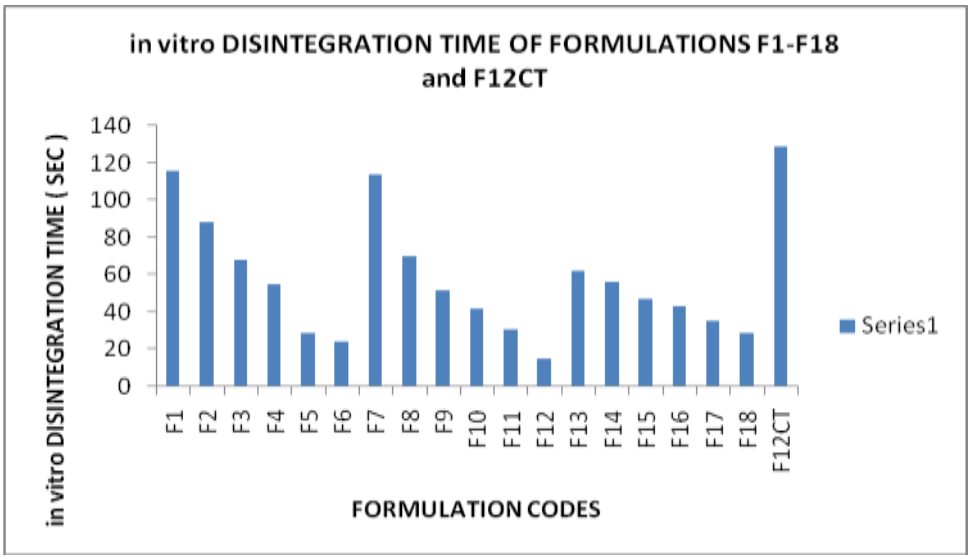

Fig. 8: *In-vitro* Disintegration Time of Venlafaxine Hydrochloride Formulations F1 to F18 and F12CT

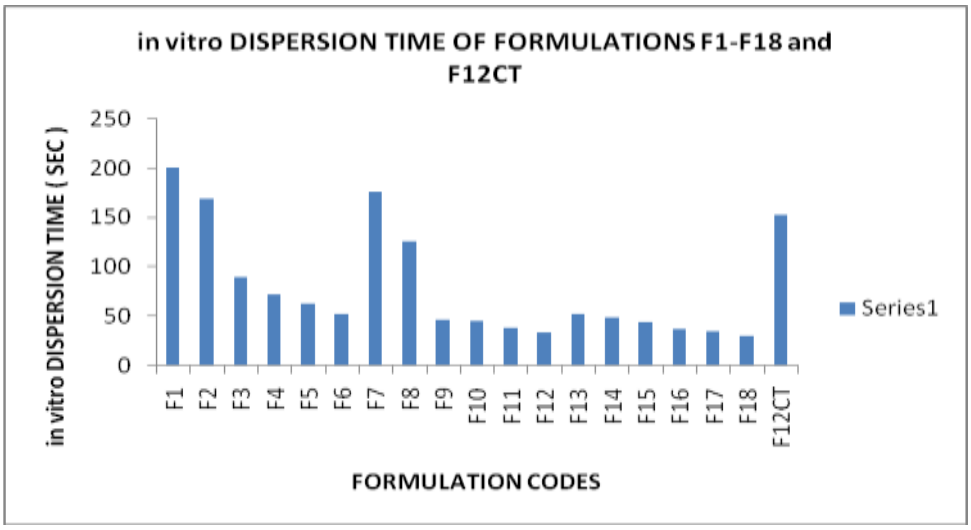

Fig. 9: *In-vitro* Dispersion Time of Venlafaxine Hydrochloride Formulations F1 to F18 And F12CT

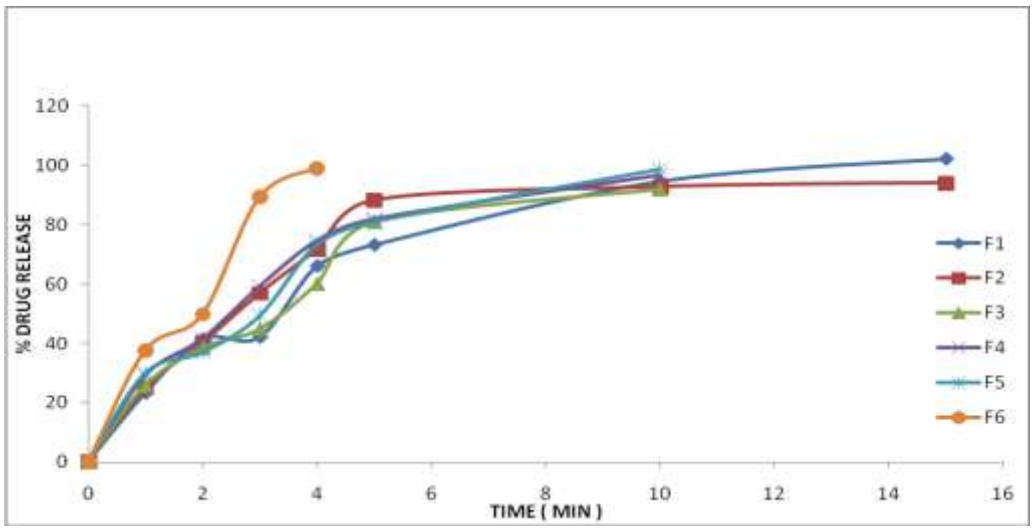

Fig. 10: Dissolution profile of Formulations F1-F6

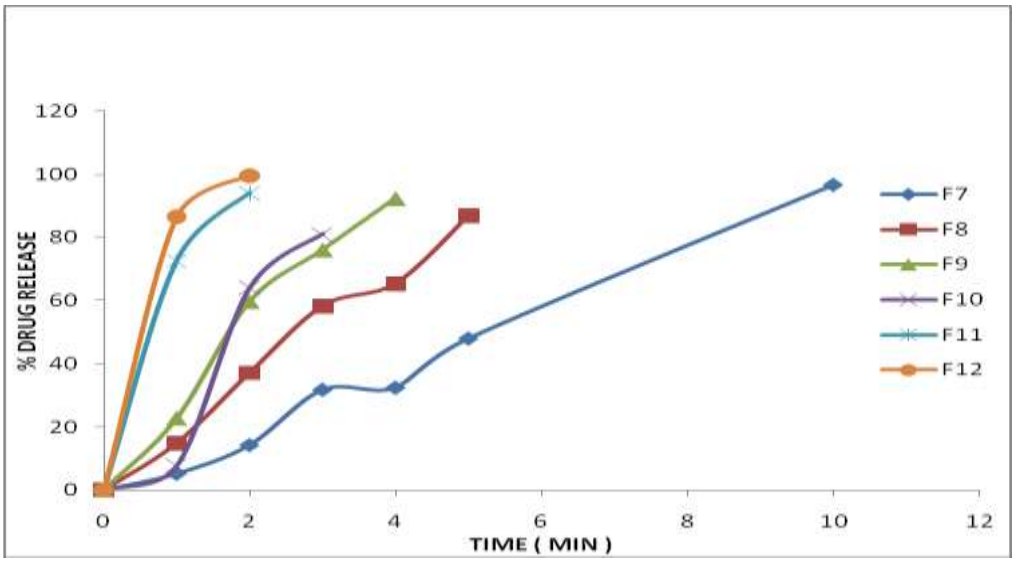

Fig. 11: Dissolution profile of Formulations F7-F12

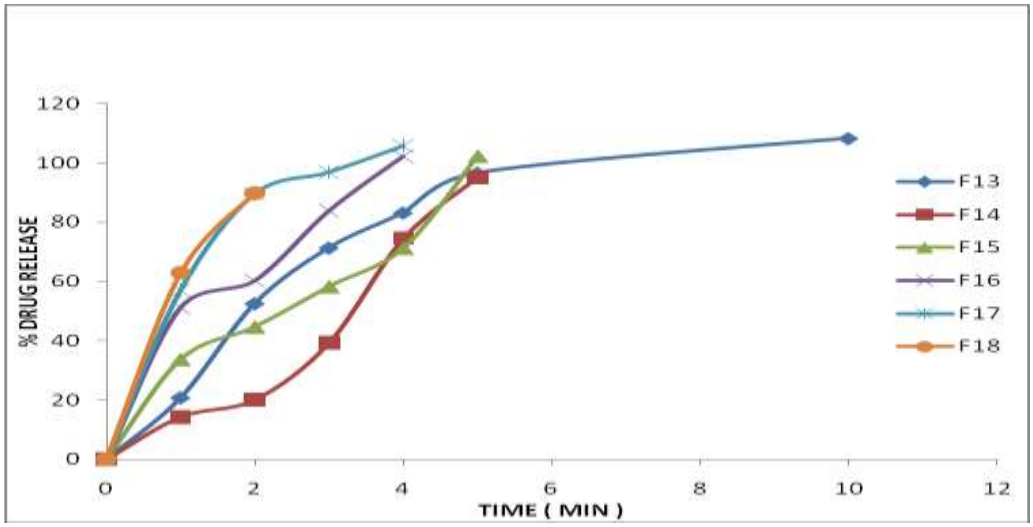

Fig. 12: Dissolution profile of Formulations F13-F18

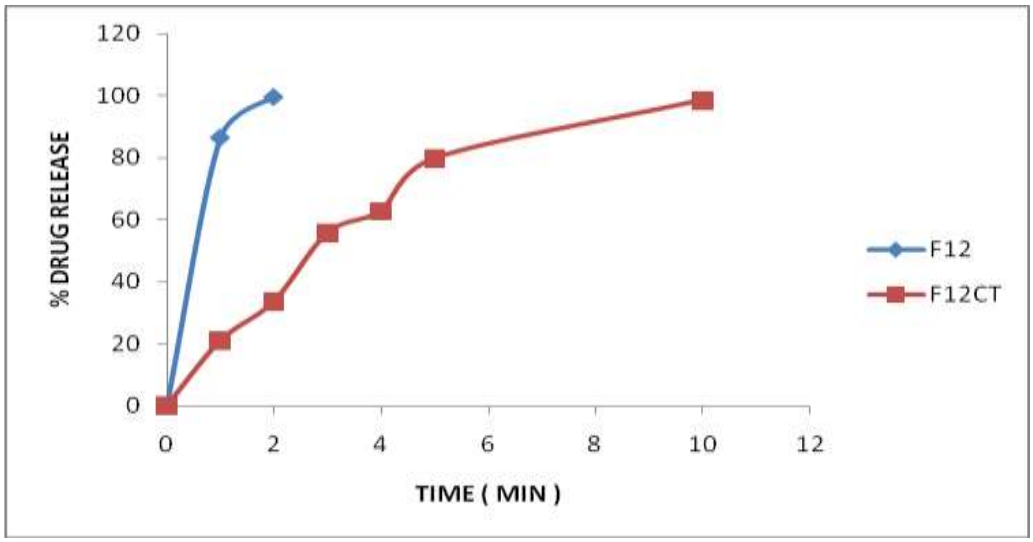

Fig. 13: Comparision of Dissolution profile of F12 and F12CT

Table 7: Regression analysis of Formulations F1 to F18

S. No.	Formulation Code	Release Kinetics				
		Zero-Order (R^2)	First-Order (R^2)	Higuchi (R^2)	Korsemeyer Peppas (R^2)	n Value
1	F1	0.871	0.985	0.967	0.950	0.621
2	F2	0.523	0.727	0.791	0.801	0.503
3	F3	0.637	0.835	0.870	0.889	0.589
4	F4	0.617	0.644	0.861	0.839	0.559
5	F5	0.843	0.967	0.958	0.935	0.576
6	F6	0.963	0.850	0.938	0.929	0.745
7	F7	0.990	0.875	0.853	0.976	0.768
8	F8	0.987	0.914	0.913	0.981	0.575
9	F9	0.975	0.947	0.935	0.959	0.614
10	F10	0.935	0.796	0.759	0.953	0.786
11	F11	0.932	0.933	0.999	0.964	0.449
12	F12	0.846	0.976	0.972	0.989	0.603
13	F13	0.972	0.975	0.948	0.982	0.949
14	F14	0.946	0.770	0.775	0.928	0.637
15	F15	0.967	0.781	0.952	0.953	0.623
16	F16	0.906	0.952	0.983	0.887	0.426
17	F17	0.894	0.991	0.988	0.946	0.499
18	F18	0.949	0.993	0.999	0.989	0.515
19	F12 CT	0.872	0.9644	0.962	0.957	0.708

CONCLUSION

Now a day the more and more research is taking place in field of MDTs and the advanced technologies are utilized in the manufacturing of MDTs. An optimized formulation Mouth Dissolving Tablets of Venlafaxine Hydrochloride was found and prepared in this study by direct compression method. The best *in-vitro* drug release observed in formulation F12 was found to be 99.59% within 2 minutes which contain the drug (Venlafaxine Hydrochloride) and superdisintegrant (Croscarmellose sodium, 6%) with other excipients. The formulation, F12 was found to be best among all other formulations because it has exhibited good wetting time, water absorption ratio and faster disintegration time with compared to all other formulations.

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