Journal of Pharmacreations

PharmaCreations

Pharmacreations | Vol.3 | Issue 4 | Oct- Dec- 2016

Journal Home page: www.pharmacreations.com

Research article *Open Access*

Formulation and development of cost effective venalfaxine hydrochloride tablets

Ch.Kishore*, N.Sriram*, E.Venkateshwarlu, A.Anil Kumar, Nagarajan. E.

**Department of Pharmaceutics, Holy Mary Institute of Technology and Science (College of Pharmacy) Bogaram, Keesara, Ranga Reddy (DT), Tselangana State.*

***Corresponding Author**: **Ch.Kishore**

Email id: pharmacykishore11@gmail.com

ABSTRACT

The present study was mainly based upon the "Process Optimization of Venlafaxine Hydrochloride tablets prepared" by wet granulation technique using different concentration of superdisintegrants. Venlafaxine, hydrochloride is a structurally novel phenethyl bicyclic antidepressant, and is usually categorized as a serotonin–norepinephrine reuptake inhibitor (SNRI) but it has been referred to as a serotonin–norepinephrine–dopamine reuptake inhibitor. The objective of the present study is to develop a pharmaceutically stable, cost effective and quality improved venlafaxine hydrochloride tablets. In the present study the main objective is directed towards development and evaluation of venlafaxine hydrochloride tablets to achieve faster dissolution to match the innovator product. It involves preformulation studies specifically compatibility studies for possible drug-excipient interactions using Fourier Transform Infrared Spectrophotometer. Evaluation of pre compression parameters. Design and development of various formulations. Evaluation of post compression parameters of the formulated tablets. To carry out in vitro drug release studies. To carryout accelerated stability studies as per ICH guidelines.

INTRODUCTION

The need for oral drug delivery system continues, due to poor patient acceptance for invasive methods, need for exploration of new market for drugs and coupled with high cost of disease management. Developing new drug delivery techniques and utilizing them in product development is critical for pharma companies to survive this century. Oral solid dosage forms such as tablets and capsules has been formulated and developed nowadays since they are most effective routes of administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Many new generations of pharmaceutical products called controlled release and sustained release drug delivery system have been developed. Although these new systems are in fast progression, for many drugs and therapeutic indications, conventional oral solid immediate release drug delivery systems provided satisfactory clinical performance with an appropriate balance of efficacy and safety [1-5].

MATERIALS AND METHODS

Venlafaxine Hydrochloride (Amoli Organics), Lactose Monohydrate (Phrmatose-200)(Merck laboratories) Microcrystalline cellulose(Avicel PH101) (SD fine chemicals), Sodium Starch Glycolate (Primogel) (SD fine chemicals), Microcrystalline cellulose (Avicel PH 102) (Merck laboratories), Magnesium Stearate (SD fine chemicals), IsoPropyl Alclohal (SD fine-chemicals limited) and all other solvents and reagents used were of analytical grade.

Table 1: Different formulations of Venlafaxine hydrochloride tablets (mg/tab)

Ingredients	F1	F2	F3	F4	F5
Intragranular part					
Venlafaxine hydrochloride	25	37.5	50	75	100
Lactose monohydrate(Pharmatose 200)	64.25	97.25	129.75	194.05	259.068
Microcrystalline cellulose (Avicel PH101)	2.5	3.0	4	6.5	9
Sodium starch glycolate(Primogel)	2	3.5	4.5	6	9.682
Iron oxide yellow(Sicovit yellow10)	0.25	0.25	0.25	0.25	0.25
Iron oxide brown	0.5	0.5	0.5	0.5	0.5
Binder solution					
Povidone USP(Kollidon)	1	1	1	1	1
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s
Extragranular parts					
Sodium starch glycolate(Primogel)	2.5	3	4	7.692	8.5
Microcrystalline cellulose (Avicel 102)	1	2	4	5	8
Magnesium stearate	1	2	2.5	4	4
CoreTotal weight (mg)	**100**	**150**	**200**	**300**	**400**

METHODOLOGY

Preparation of venlafaxine hydrochloride tablets

Intra-granulation

Sifting [33]

Venlafaxine hydrochloride, microcrystaline cellulose, sodium starch glycolate, lactose monohydrate sifted through 30 mesh. Iron oxide yellow, iron oxide brown sifted through 100 mesh. povidone sifted through 30 mesh.

Granulation

Dry mixing

Transferred the sifted material from step-1 into the rapid mixer granulator and mixed for 10 minutes by setting impeller at slow rpm and chopper set to "off". Which unit dose samples collected after 15 min of mixing interval.

Binder solution preparation

Binder solution was prepared by dissolving povidone k30in isopropyl alcohol.

Wet granulation

Binder solution was added slowly to the step-2a dry mix by setting impeller at slow rpm and chopper set to "on".
Impeller speed – 200 rpm
Chopper speed – 1000 rpm

Wet screening

After completion of addition of binder solution, wet granulate was raked and kneaded till to get wet granulate with desired consistency is reached.

Drying

Dry the wet granulate in fluid bed dryer at an inlet temperature of 50° - 60°C LOD was checked at 80°C with IR moisture analyzer in automatic mode & was found to be 1.38-1.55% w/w against the limit of NMT 2% w/w.Air drying of wet mass done in all batches for 10 minutes [6].

Dry screening (vibro sifter & multimill)

Sifted the dried granules through # 30 sieve and collected the oversized granules separately. Milled the oversized granules using 1.0 mm screen at medium speed with knives forward and passed through # 30 sieve [7].

Compression

Granules prepared from above process are subjected for making of tablets. Tablets were compressed using compression machine with lubricated blend, employing appropriate punch tooling. Collect the compressed tablets in double poly lined bag and proceeded for coating.

Table 2: Description of dies and punches

Parameters	Standards
Lower punch	8.73×8.5 mm round standard concave plain
Upper punch	8.73×8.5 mm round standard concave plain
Dies	8.73×8.5 mm round standard concave plain

TABLET COATING

Preparation of coating suspension

Take weighed quantity of purified water in S.S. vessel and heat the water. Add & dissolve weighed batch quantity of iron oxide yellow,iron oxide brown colour sample into the above solution depending upon the tablet strength under stirring to avoid any lump formation. Complete the addition within 5-10 min under stirring. Continue stirring for 45 minutes and filter the solution through 100 mesh**.** Complete coating until the average weight gain is 2% of uncoated Table average weight [33]

EVALUATION PARAMETERS

Thickness

The thickness of tablets was determined by using digital vernier calipers. Ten individual tablets from each batch were used and the results averaged. It should be in a range of ±5% variation of a standard value. The results were expressed in mm.

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation were calculated. The test for weight variation is passed only if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown.

Hardness

Ten tablets from each batch were selected and hardness was measured using Digital hardness tester to find the average tablet hardness or crushing strength.

Hardness should be in between 3-6 kg/cm^2.

Friability

The friability values of the tablets were determined using a roche friabilator. It is expressed in %. 20 tablets were initially weighed (initial weight) and transferred to friabilator. Friabilator was operated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

$$\text{Friability} = \frac{Wo - W}{Wo} \times 100$$

Friability of tablets less than 1% was considered acceptable.

Disintegration Time

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37°C and observed over the time described in the individual monograph. To fully satisfy the test the tablets disintegrate completely into a soft mass having no palpably firm core. Immediate release tablet should be able to release the drug with in 3 min [7-10].

ASSAY

Assay of venlafaxine hydrochloride by HPLC

Mobile phase preparation

The mobile phase contained 35% buffer &65% acetonitrile &delivered at a rate of 0.6ml/min.an accurately weighed 7gm of potassium dihydrogen phosphate transferred to 1000ml of water & adjusted to P^H to 3 with orthophosphoric acid .Before use,the mobile phase was degassed by an ultrasonic bath &filtered through a 0.45 nylon filter.

Diluent preparation

Phosphate buffer of pH 6.8 is used as a diluent.

In vitro dissolution test

The dissolution studies of the prepared tablets were carried using Electro lab apparatus II. Dissolution was performed in 900 ml phosphate buffer of pH 6.8 at 37 ± 0.5°C at 100 rpm. An auto sampler, coupled to the dissolution apparatus was programmed to withdraw and replace 10 ml of the dissolution media at 0, 5, 10, 15, and 30,45 &60 min. About 80% of the drug should be released within 30 min.

Dissolution parameters

Medium : Phosphate buffer, pH 6.8
Volume : 900 ml
Apparatus : Dissolution apparatus type II of USP (paddle)
Rotation speed : 75 rpm
Temperature : 37 ±0.5°C
Time : 45 min

Preparation of standard solution

25 mg of venlafaxine hydrochloride, working standard was weighed and transferred to 100 ml volumetric flask. 60 ml of methanol was added and sonicated to dissolve the content for 15 min. 1 ml of the above solution was taken and 50 ml of media was added. The above solution was filtered through 0.45 µ nylon membrane filter paper.

Preparation of sample solution

Set the dissolution test apparatus as per above conditions. Place one tablet each in six dissolution bowl. Run the apparatus for 45 min. Withdraw 10 ml of sample in above time intervals from each bowl, replacing the same amount every time with fresh dissolution medium. Filter the solution through 0.45 µ nylon membrane filter paper.

PROCEDURE

Preparation of buffers and reagents

Sodium hydroxide (NaOH 0.2M) solution

8gms of NaOH was taken in a 1000ml volumetric flask containing about 700ml of distilled water &volume was made to the mark with distilled water.

Pottosium dihydrogen phosphate (0.2M) solution

Pottosium dihydrogen orthophosphate (27.218gm) was added in 1000ml volumetric flask containing about 700ml of distilled water &volume was made to the mark with distilled water.

Phosphate buffer (P^H 6.8) solution

50ml of 0.2M Pottosium dihydrogen orthophosphate solution was taken in a 200ml of volumetric flask, to which 22.4ml of 0.2M NaOH solution was added. Then volume was made to the mark with distilled water & P^H was adjusted to 6.8 with dilute NaOH solution.

% labeled amount of Venlafaxine hydrochloride dissolved

$$= \frac{AT}{AS} \times \frac{W_S}{100} \times \frac{5}{100} \times \frac{900}{100} \times \frac{P}{\text{label claim in mg}} \times 100$$

Where,
AT = peak area of venlafaxine hydrochloride, in sample solution
AS = average peak area of venlafaxine hydrochloride, in standard solution.
Ws = Weight of venlafaxine hydrochloride, working standard taken in mg.
P = potency.

COMPARISION WITH MARKETED FORMULATION [61]

Data treatment

Similarity factor (f2)

As the name specifies, it stresses on the comparison of closeness of two comparative formulations. Generally similarity factor in the range of 50-100 is acceptable according to USFDA. It can be computated using the formula:

$$f2= 50\times\log \{[1+ (1/n) \Sigma_{t=1}^{n} (R_t-T_t)^2]^{-0.5} \times 100\}$$

Where, n is the number of dissolution sample times, R_t and T_t are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles, respectively. The similarity factor should be between 0 and 100. It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases.

Difference factor (f1)

Difference factor focuses on the difference in percent dissolved between reference and test at various time intervals. It can be mathematically computed by using the formula:

$$f1= \{[\Sigma_{t=1}^{n} |R_t-T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$$

Therefore the factors directly compare the difference between percent drug dissolved per unit time for a test and a reference product. Similarity factor of 50-100 ensures sameness of two products.

Difference factor of 0-15 ensures minor difference between two products. Prior to in vivo study, comparison of in vitro dissolution profiles using similarity and difference factors may be the promising surrogate.

Accelerated stability studies

The design of the formal stability studies for the drug product was based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance. Specification which is the list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications. The selected batch was kept at 40°C with 75% RH and the samples were withdrawn at first, second, third and six months for physical and in vitro evaluation of drug release.

When significant change occurs at any time during six months testing at the accelerated storage conditions, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria

In general significant change for a drug product is defined as:

- A 5% change in assay from its initial value or failure to meet the acceptance criteria for when using biological or immunological procedures
- Any degradation products exceeding its acceptance criterion
- Failure to meet the acceptance criterion for appearance, physical attributes, and functionality test. e.g. hardness, dose delivery per actuation, however some changes in physical attributes may be accepted under accelerated condition and as appropriate for the dosage form
- Failure to meet the acceptance criterion for pH
- Failure to meet the acceptance criterion for dissolution for 12 dosage units.

RESULTS AND DISCUSSION

Drug identification

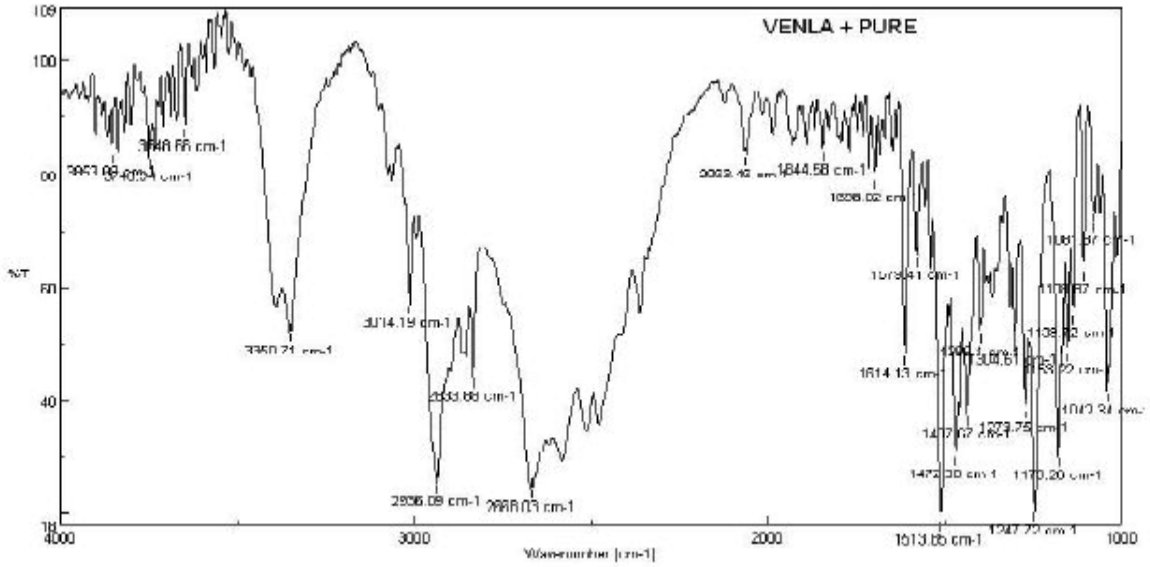

Figure No 1: FTIR spectrum of Venlafaxine hydrochloride

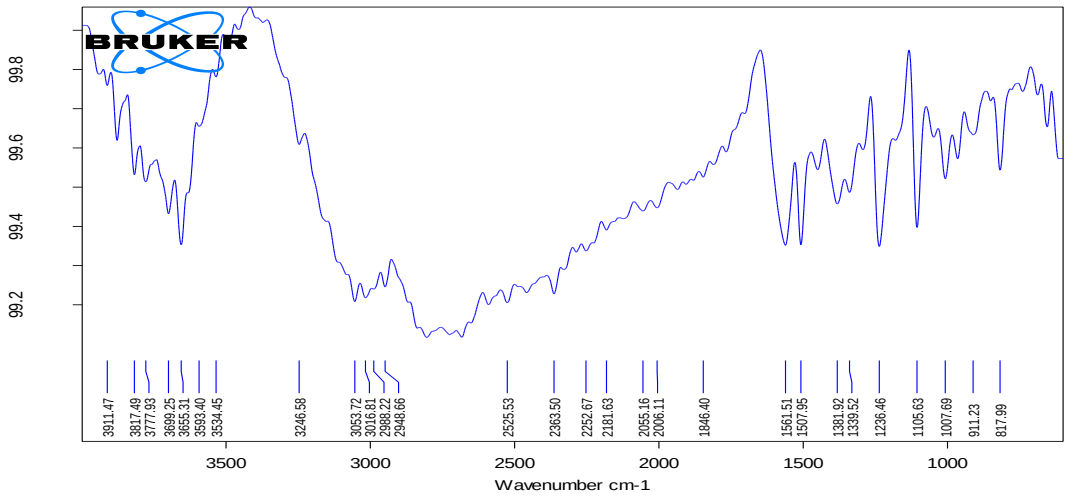

Figure No 2: FTIR Spectrum of Optimized Formulation

Evaluation of tablet blend

Evaluation of pre compression parameters

Table No 3: Physical properties of granules for different trail batches

S.no	Loss On Drying (%W/W)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio	angle of repose(°)
1	1.55	0.53	0.71	25.35	1.339	28.83
2	1.48	0.55	0.68	20.00	1.236	26.51
3	1.45	0.46	0.60	23.14	1.280	25.54
4	1.38	0.47	0.60	21.70	1.276	25.90
5	1.40	0.50	0.65	23	1.30	25

Mean ± S.D, n=6

COMPRESSION PARAMETERS

Evaluation of tablets

Dissolution

Table 4: Dissolution profiles of Venlafaxine hydrochloride tablets trial batches from F1 toS F5 in 6.8 pH phosphate buffer

Time (Min)	Cumulative % drug release					
	F1	F2	F3	F4	F5	Innovator
0	0.00±*0.00*	0.00±*0.00*	0.00±*0.00*	0.00±*0.00*	0.00±*0.00*	0.00±*0.00*
5	20.9±*1.2*	21.3±*1.4*	36.6±*1.5*	38.5±*2.2*	50.5±*2.4*	49.0±*2.8*
10	38.2±*1.3*	34.5±*2.2*	48.9±*1.6*	40.3±*2.4*	58.3±*2.6*	54.6±*3.2*
15	48.5±*1.5*	46.1±*3.2*	51.2±*2.2*	55.2±*3.2*	71.2±*2.0*	69.2±*3.2*
30	59.5±*1.2*	60.4±*2.0*	71.2±*3.3*	68.2±*1.4*	80.5±*1.6*	70.2±*3.2*
45	71.1±*1.3*	73.5±*2.2*	82.5±*3.2*	84.5±*2.8*	89.6±*3.4*	84.9±*2.5*
60	84.5±*1.2*	89.6±*2.2*	90.2±*3.2*	93.5±*2.2*	101.5±*2.2*	100±*3.2*

Mean ± S.D, n =6.

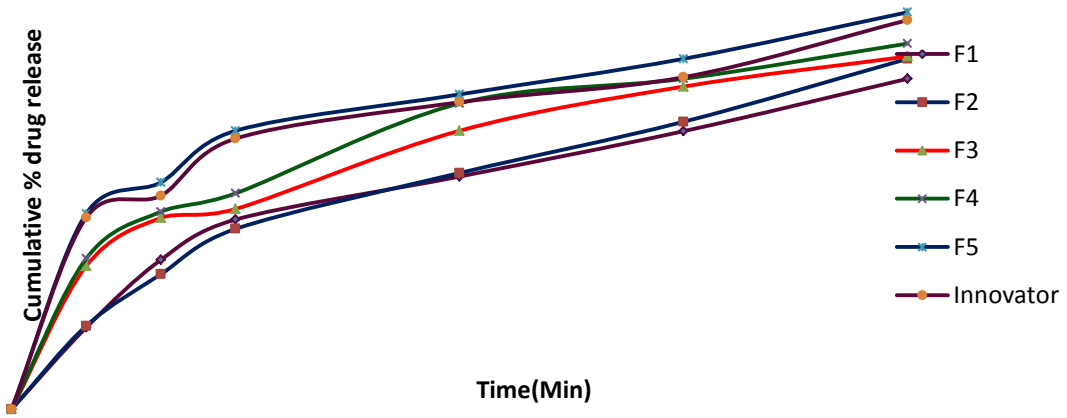

Figure 3: Graphical representation of dissolution profiles of F1- F5 and Comparison with Innovator.

DISCUSSION

The present study was mainly based upon the "Process Optimization of Venlafaxine Hydrochloride tablets prepared" by wet granulation technique using different concentration of superdisintegrants. The main goals of treatment in depression are relief of symptoms, slowing progression of the disease, and reduction of future events. All the results related to design and *in vitro* evaluation of oral Immediate release tablets of Venlafaxine Hydrochloride and its comparative *in-vitro* drug release study with marketed product of Venlafaxine Hydrochloride were analysed and the Venlafaxine Hydrochloride tablet seem to be a successful formulation.

In vitro drug release

(Shown in table 24&25&26 and figure 13,14&15)

- Formulations F1 to which 25mg Venlafaxine HCL &4.5mg Sodium Starch Glycolate were added showed more than 85% of drug release within 60 min which confirms within the limits by USP, which states that not less than 80% of labeled amount of Venlafaxine HCL was released in 45min. This phenomenon due to Sodium Starch Glycolate is found to release the drug by swelling mechanism. SSG swells 7-12 folds in less than 30 seconds that is too much swelling takes place in three dimensions.

- F2 to which 37.5mg Venlafaxine HCL &6.5mg Sodium Starch Glycolate were added showed more than 85% of drug release within 60 min. which confirms within the limits by USP, which states that not less than 80% of labeled amount of Venlafaxine HCL was released in 45min. This phenomenon due to SSG is found to release the drug by swelling mechanism. Sodium Starch Glycolate swells 7-12 folds in less than 30 seconds that is too much swelling takes place in three dimensions.
- For formulations F3 to which 50mg Venlafaxine HCL & 8.5mg Sodium Starch Glycolate were added showed in vitro drug release more than 85% within 60 min. & F4 to which 75mg Venlafaxine HCL & 13.69mg Sodium Starch Glycolate were added showed in vitro drug release more than 92% within 60min. This phenomenon due to Sodium Starch Glycolate is found to release the drug by swelling mechanism. SSG swells 7-12 folds in less than 30 seconds that is too much swelling takes place in three dimensions.
- For formulations F5 to which 100 mg Venlafaxine HCL,18.182mgSodium Starch Glycolate were added showed in vitro drug release more than 95% within 60min. This phenomenon due to Sodium Starch Glycolate is found to release the drug by swelling mechanism. Sodium Starch Glycolate swells 7-12 folds in less than 30 seconds that is too much swelling takes place in three dimensions.

SUMMARY

- The present study was mainly based upon the "Process optimization of venlafaxine hydrochloride 25mg,37.5mg,50mg,75mg,100mg tablets" (Antidepressants, Serotonin Uptake Inhibitors) by Wet Granulation Technique. Various formulations of venlafaxine hydrochloride tablets were prepared by using different proportion & combination of Excipients. Tablet blends were prepared and micromeritic studies were carried out for those blends. Precompressional parameters such as angle of repose, bulk density, tapped density, hauser's ratio, compressibility index for physical mixtures of formulations (F1 – F4) were evaluated and results were reported. From the results obtained by UV, the calibration curve was constructed having regression value of 0.999.
- Assay values of the formulations were observed in the range of 98 to 102%. Compatibility studies were performed and it was observed that all the ingredients used were compatible with the drug. Formulation (F5) was formulated by including 9mg of sodium starch glycolate. The results showed disintegration was within limits and 100% drug release was found in 45min. So, formulation (F5) was taken as optimized formulation. Accelerated stability studies were performed for this batch. Assay and Dissolution studies were performed for the optimized formulation (F-5) at different time intervals. All the parameters were found to be satisfactory. Dissolution studies were performed and it was found that formulation F5 have shown best results and comparable with the innovator.

CONCLUSION

From the above experimental results it can be concluded that process optimization of venlafaxine hydrochloride 25mg, 37.5mg, 50mg, 75mg, 100mg tablets can be prepared by wet granulation method using different concentration of superdisintegrant. Tablet blends were prepared and micromeritic studies were carried out for those blends. Compatibility studies were carried out and found that drug and excipients are compatable with each other. Formulation (F5) containing 9mg of sodium starch glycolate was found to have closeness to the innovator product from similarity and difference factor which was found to be 84.29 and 0.81 respectively. Also dissolution data of all formulations reveals that as concentration of superdisintegrant increases the percentage drug release was found to be increased. Formulation (F5) containing high percentage of sodium starch glycolate shows that the disintegration was within limits and 100% drug release was found in 45 min. So, formulation (F5) was taken as optimized formulation. For the formulation F5, there was no significant change in physical appearance, hardness, friability, disintegration time, assay and dissolution even after three months of stability study.

BIBLIOGRAPHY

[1]. Sastry SV, Nyshadham JR, Fix JA. Recent Technological Advances in oral drug delivery Pharm Sci Tech Today 3(4), 2000, 138-45.
[2]. Bhowmik D, Chiranjib B, kanth K, pankaj, chandira RM. Fast dissolving tablets. J Pharm Res 1(1), 2009, 163-77.
[3]. Shargel L, Kanfer I. Generic Drug Product Development of solid oral dosage forms. Winley Inter Science 2010, 1-16.
[4]. Harbir K. Processing technologies for pharmaceutical tablets. IRJP 3(7), 2012.
[5]. Silpa SK, Kumar MA, Garigeyi P. Formulation and optimization of clopidogrel bisulfate IR tablet. IJPFR oct-dec 1(3), 2012, 56-72
[6]. Holliday SM, Benfield P. Venlafaxine: A review of its pharmacology and therapeutic potential in depression drugs. Drugs 49, 1995, 280-94.
[7]. Muth EA, Haskins JT, Moyer JA, Husbands GE. Antidepressant biochemical profile of the novel bicyclic compound Wy-45,030, an ether cyclohexanol derivative. Biochem Pharmacol 35, 1986, 4493-7
[8]. Troy SM, Parker VD, Fruncillo RJ, Chiang ST. The pharmacokinetics of venlafaxine when given in a twice-daily regimen. J Clin Pharmacol 35, 1995, 404-9.
[9]. Subramaniam Kannan performed Studies on process optimization of levofloxacin hemihydrates tablets 265, 2010, 36-99.
[10]. Shailesh Sharma have Developed and optimized fast-dissolving tablets of Promethazine Theoclate tablets 15, 2011, 45-95.