

EVALUATION OF PHYTOCHEMICAL SCREENING AND THROMBOLYTIC ACTIVITY OF HYDRO ALCOHOLIC EXTRACT OF SOLANUM TORVUM FRUITS

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Received: July 15, 2025

Accepted: Aug 10, 2025

Published: Aug 13, 2025

Abstract:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. The active pharmaceutical ingredient Venlafaxine Hydrochloride was subjected to preformulation study, which encompasses the “Accelerated drug excipient compatibility study”, and the results obtained with selected excipients showed good compatibility with Venlafaxine Hydrochloride drug. Venlafaxine Hydrochloride coated pellets were formulated by using commercially available sugar pellets and Venlafaxine Hydrochloride SR coated capsules were filled by automatic capsule filling machine with various excipients used during formulation. The optimization procedures aided in the stabilization of the formula and in the formulation of the Venlafaxine Hydrochloride modified release capsules.

Key words: Venlafaxine Hydrochloride, DDS, Sustained release.

INTRODUCTION:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientists to develop controlled release system.

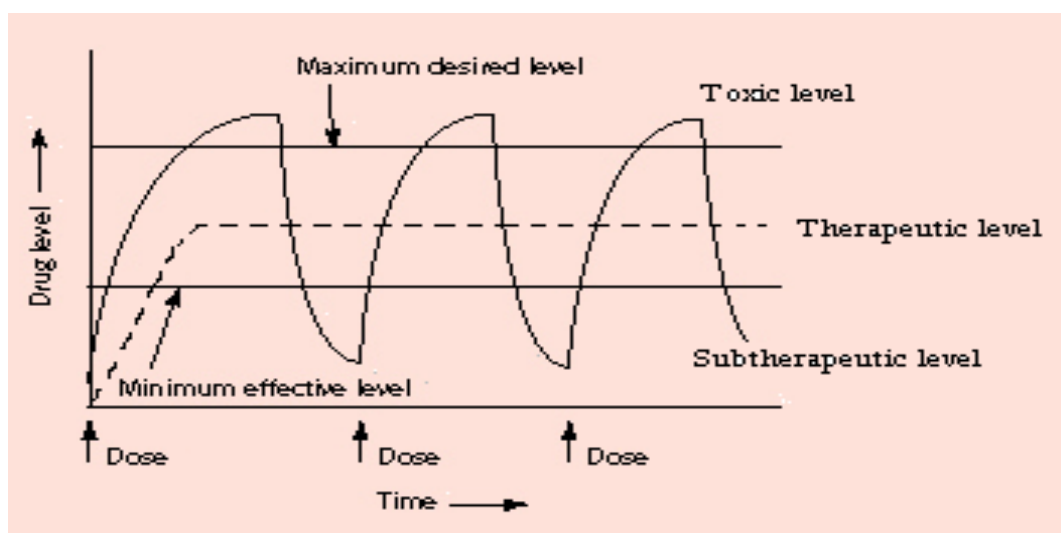


FIG:1 Plot Between Drug Release Level & Time

The design of oral sustain drug delivery system should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.

Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or require strict compliance or

long-term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Classification modified release drug delivery system:

A) Delayed release

B) Sustained release

Controlled release

Extended release

C) Site specific targeting

D) Receptor targeting

A) Delayed Release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Sustained release:

During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor such as the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the

technology of sustained release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

1) Controlled Release:

These system include any pharmaceutical dosage forms that achieves slow release of drug over an extended period of time.

2) Extended Release:

The system include any pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

C) Site specific targeting:

These system refers, targeting a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting:

These system refer, targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

Potential advantages and disadvantages of sustained release dosage forms

Advantages:

- Avoid patient compliance problems.
- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Obtain less potentiation or reduction in drug activity with chronic use.

- Minimize drug accumulation with chronic dosing.
- Improve efficiency in treatment.
- Cure or control condition more promptly.
- Reduction in fluctuation of blood drug level.
- Improve bioavailability of some drugs.
- Make use of special effects, e.g. sustained-release aspirin for morning relief of arthritis by dosing before bedtime.
- SR drug delivery system aims at optimized therapy constant blood levels.
- Constant blood levels achieved with desired effect and this effect is maintained for an intended period of time.
- Drugs susceptible to enzymatic inactivation or by bacterial decomposition can be protected by encapsulation in polymer system suitable for SR.
- For drugs having specific window for absorption increased bioavailability can be attained by localizing the SR in that particular region of the GIT.
- Economy

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORMS:

- They are costly.
- Increased variability among dosage units
- Dose dumping

Limited choice of selecting desired dose in the unit:

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

Poor In Vitro – In Vivo correlation:

In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here so called '*Absorption window*' becomes important and may give rise to un-satisfactory drug absorption in in-vivo despite excellent in in-vitro release.

Patient variation:

The time period required for absorption of drug, released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

CAPSULES:

Capsules are defined as unit solid dosage form of medicaments available as small containers (shell) made up of gelatin enclosing accurately measured drug substance.

The term capsule is derived from the Latin word *CAPSULA* meaning a small container. Capsules occupy a significant position in the drug development. They are often believed as the primary oral dosage form because of their simple manufacturing process compared to other oral dosage forms. Gelatin has the property of disintegrating when it comes contact with water, thereby releasing the medicament completely. Instead of gelatin, denatured gelatin, methyl cellulose and polyvinyl alcohol can also be used to make the capsule shells.

Capsules are broadly divided into two types based on the composition of gelatin.

Hard gelatin capsules.

Soft gelatin capsules.

HARD GELATIN CAPSULES:

Hard gelatin capsules are also known as dry- filled capsules or two pieces capsules. A large number of capsules manufactured by the pharmaceutical companies are hard gelatin capsules. Hard gelatin capsules consists of two parts known as capsule body and the capsule cap. The drug substance is placed in the body and the cap is slid over it, hence enclosing the drug substance.

Theory of pellet formation and growth:

Before selection and optimization of any Pelletization/granulation process, it is important to understand the fundamental mechanisms of pellet formation and growth.

Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are derived by visual observations. Out of these hypothetical theories the most convincing classification of Pelletization process, involves three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer 14. Nucleation is a stage of Pelletization process that occurs whenever a powder is wetted with solvent system. The primitive particles are drawn together to form three-phase air-water-liquid nuclei system which are held together by liquid bridges that are pendular in nature. The reduction of particle size will improve the bonding strength between them. Further the size, the rate and the extent of nuclear formation depends upon the size of the particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates.

REVIEW OF LITERATURE

DR.A.Senthil*, Chauhan Pratik Navinchandra et al.,2012, developed the present study for the formulation and evaluation of buccal patches of venlafaxine hydrochloride using sodium alginate with various hydrophilic polymers like carbopol 934 P, carboxymethyl cellulose and HPMC K4M in various proportions and combinations were fabricated by solvent casting technique. An in-vivo muco-adhesive parameters and in vitro drug release parameters were evaluated. All these fabricated patches were sustained for 10hrs and obeyed first order release kinetics.

Inampundi Ajit*, Adimoolam Senthil,et al.,2012, developed this study for the formulation and development of buccal tablets of Venlafaxine HCL. Buccal route is excellent for the systemic delivery, thereby rendering great bio-availability. Tablets of Venlafaxine HCL were prepared by direct compression method. Various concentrations of bio-adhesive polymers like hydroxypropylmethylcellulose K4M(HPMC K4M), carboxymethylcellulose (CMC), carbopol 934P and chiton. The tablet were evaluated for in-vitro release in pH 6.8 phosphate buffer for 8 hours in standard dissolution apparatus in order to determine the mode of release, the data was subjected to model fitting, the optimized formula followed non-fickian release mechanism with zero order kinetics. The formulation

containing Venlafaxine HCL and HPMC K4M in the ratio of 1:1 could be used to design effective and stable buccoadhesive tablets of Venlafaxine HCl .

Liu Y, Sun Y et al.,2012., prepared a different venlafaxine hydrochloride sustained-release products and to elucidate the influence of composition of the coating film on the in vitro drug release profiles and in vivo pharmacokinetics. Pellets were prepared by a standardized process of extrusion/spheronization. A selected fraction size (0.8-1.0 mm diameter) of pellets of each formulation was coated with Eudragit NE30D or ethylcellulose. The results suggested that Formulation 1 and Formulation 2 both had better bioavailability compared with Effexor XR.

Akelesh T*, Rakesh S et al.,2011, developed this pharmaceutically equivalent, stable, cost effective and quality improved formulation of Venlafaxine HCl pellets it in the form of sustained release capsule and compare with that of the marketed dosage form. In the present work the preparation of pellets containing different polymers has been investigated. Among the different formulations prepared, formulation no.10 coated with ethyl cellulose N-50 4.5%, Hydroxy propyl methyl cellulose 15%, Steric acid 5%, was found be satisfactory. Sustained Release capsule from formulation no10 gave satisfactory dissolution profile.

C Vijaya, Manasa Bingi, LV Vingneshwaran et al .,2011, states that the transdermal delivery of venlafaxine hydrochloride (VHCl) may result in proper patient compliance by reducing the incidence of the undesirable GI problems generally associated with its plural oral dosing. The present study is an attempt to investigate the improvement of the transdermal flux of the hydrophilic VHCl by certain permeation enhancers viz. glycerin, urea, propylene glycol and mixture of propylene glycol and ethanol across pig ear skin. The results of the present study indicate that the inclusion of mixture of permeation enhancers, Propylene glycol and ethanol may make the transdermal delivery of VHCl feasible.

Guan, Tingting · Wang et al.,2011, studied this comparative stability of venlafaxine hydrochloride (VEN) sustained-release pellets prepared by double-polymer coatings and hot-melt subcoating combined Eudragit® NE30D outercoating. The uncoated VEN pellets, containing 45% (w/w) VEN, 45% (w/w) MCC (PH101), 10% (w/w) stearic acid and 0.5% (w/w) Carbopol974, were prepared by extrusion-spheronization.

SCOPE AND OBJECTIVE

Aim of the present research study is to develop VENLAFAXINE HYDROCHLORIDE extended release coated pellets using Ethyl cellulose, Eudragit(dependent and independent), Surelease by using drug layering solution method by pelletization technique.

Venlafaxine is used primarily for the treatment of depression, general anxiety disorder, social phobia, panic disorder, and vasomotor symptoms. Venlafaxine is well absorbed and extensively metabolized in the liver. Venlafaxine half-life is 5 ± 2 hours. These biopharmaceutical and physicochemical properties reveal that venlafaxine is an ideal candidate to develop into extended release pellets.

Objective of present study is to formulate, Venlafaxine hydrochloride ER pellets to observe the dissolution profile of the polymers in regard with the drug.

Rational for the selection of dosage form is to minimize variation in residence time, less susceptible to dose dumping, facilitate accurate delivery of small quantity of potent drug, reduced potential side effects without lowering drug bio-availability

Rational use for the development of antidepressant venlafaxine has a unique chemical structure and neuropharmacologic profile. It significantly inhibits reuptake of both serotonin and nor epinephrine and lacks notable muscarinic-cholinergic or alpha-adrenergic effects. It is so can be formulated by pelletization method also.

Target of our study is to formulate the Sustained release Venlafaxine hydrochloride pellets by drug layering solution method and improve the release rate of the drug by 20 hours and compare with the reference product. To achieve this goal we have to formulate and evaluate the pellets & capsules. The formula will be finalized by comparing the in-vitro dissolution profile with that of the reference product.

PLAN AND SCOPE OF THE WORK

Objective of the study is to produce Extended release coated pellets dosage form using Venlafaxine Hydrochloride. It is achieved by doing pre-formulation, formulation and evaluation, and stability studies for the drug and the excipients.

A) Pre-Formulation Studies:

1. Active pharmaceutical ingredient profile study.
2. Excipient profile study.
3. Characterization of active pharmaceutical ingredient and polymer using FT-IR.
4. Thermal analysis for characterizing interaction between drug and excipients.
5. Analysis of excipients compatibility by stability studies.

B) Formulation and evaluation:**Fabrication of sugar core pellets and sustained release coated pellets:**

1. Formulation of Venlafaxine hydrochloride SR coated pellets.
2. Evaluation of Venlafaxine hydrochloride sugar coated pellets.
3. Evaluation of Venlafaxine hydrochloride SR coated pellets.
4. Evaluation of Venlafaxine hydrochloride SR coated Capsules.

C) Stability study of Sustained release coated pellets.**D) Comparison with reference sample.****MATERIALS AND EQUIPMENTS****TABLE 3: List of Materials**

Venlafaxine Hydrochloride	Ra chem, Hyderabad
Sugar Spheres#20	Meghana, Hyderabad
Aerosil	Sigma Aldrich, Bangalore

Surcose	Sigma Aldrich, Bangalore
Hypromellose	Sigma Aldrich, Bangalore
Eudragit	Basf, Germany
Surelease	Basf, Germany
Ethyl cellulose	Feicheing, E
Poly Ethylene Gylcol-6000	Clariant
Magnesium stearate	Sigma Aldrich,Bangalore
Isopropyl Alcohol	Rankem
Purified water	In House

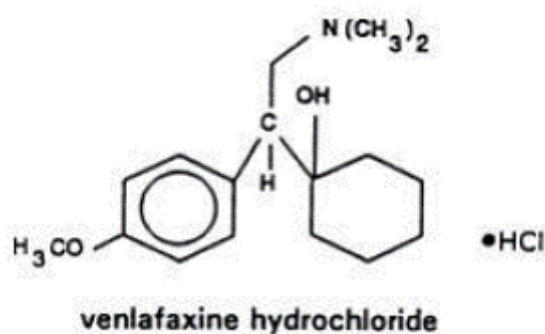
DRUG PROFILE

ACTIVE PHARMACEUTICAL INGREDIENT PROFILE:

Venlafaxine Hydrochloride:

Therapeutic category:

Antidepressant drug.

Structure:**FIG: 17****Chemical name:**

(*RS*)-1-[2-dimethylamino-1-(4-methoxyphenyl) - ethyl] cyclohexanol

Molecular weight:

313.87g/ml

Molecular formula:

$C_{17}H_{27}NO_2 \cdot HCl$

Description:

It is a white to off-white crystalline solid.

Appearance:

White crystal

Solubility:

It is having solubility of 572 mg/ml in water. Its octane: water partition co-efficient is 0.43.

Melting point:

Melts between 215 to 217 degrees

Loss of drying:

1.0% maximum is determined.

Heavy metals:

Maximum 20 ppm

Mechanism of action:

Venlafaxine is a bi-cyclic antidepressant, and is usually categorized as a serotonin-nor-epinephrine reuptake inhibitor (SNRI), but it has been referred to as a serotonin-nor-epinephrine-dopamine reuptake inhibitor (SNDRI). It works by blocking the transporter "reuptake" proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitters in the synapse. The neurotransmitters affected are serotonin and nor-epinephrine. Additionally, in high doses it weakly inhibits the reuptake of dopamine, with recent evidence showing that the nor-epinephrine transporter also transports some dopamine as well, since dopamine is inactivated by nor-epinephrine reuptake in the frontal cortex, which largely lacks dopamine transporters: therefore, venlafaxine can increase dopamine neurotransmission in this part of the brain.

Pharmacokinetic properties

Venlafaxine is well absorbed, with at least 92% of an oral dose being absorbed into systemic circulation. It is extensively metabolized in the liver via the CYP2D6 isoenzyme to desvenlafaxine (*O-desmethylvenlafaxine*), which is just as potent a serotonin-nor-epinephrine reuptake inhibitor as the parent compound, meaning that the differences in metabolism between extensive and poor metabolizers are not clinically important in terms of efficacy. Side effects, however, are reported to be more severe in CYP2D6 poor metabolizers. Steady-state concentrations of venlafaxine and its metabolite are attained in the blood within 3 days. Therapeutic effects are usually achieved within 3 to 4 weeks. No accumulation of venlafaxine has been observed during chronic administration in healthy subjects. The primary route of excretion of venlafaxine and its metabolites is via the kidneys. The half-life of venlafaxine is relatively short, and, therefore, patients are directed to adhere to a strict medication routine, avoiding missing a dose. Even a single missed dose can result in the withdrawal symptoms.

Pharmacodynamic properties

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiating activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, *O-desmethylvenlafaxine* (ODV), are potent inhibitors

of neuronal serotonin and nor epinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic cholinergic, H1-histaminergic, or α 1-adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Dose: 75 to 150mg daily, in divided doses.

METHODOLOGY AND EVALUATION

Preformulation Studies

Objective

The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.

Reasons For Preformulation Studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first in the rational development of dosage forms

Scope: The use of Preformulation parameters maximizes the chances in formulating an acceptable, safe efficacious and stable product.

Physical Properties

For a drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug.

Determination Of Bulk Density And Tapped Density

Bulk density is the ratio of the weight of a powder to the volume it occupies. It is expressed as gm/ml. Volume occupied by powder includes volume of the solid portion of the particle and voids between the particles. Bulk density is important in determining the size of the containers needed for handling and processing

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density, and tapped density were calculated using the following formulas:

$$\text{Bulk density} = W / V_o$$

Compressibility Index

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size of a powder.

Table 7.1 Compressibility Index Range

S. No.	% compressibility index	Flowability
1	5-15	Excellent
2	12-18	Good
3	18-21	Fair-passable
4	23-35	Poor
5	33-38	Very poor
6	<40	Very Very Poor

Compressibility index were calculated using the formula:

$$\text{Compressibility index} = \frac{T.D - B.D}{T.D} \times 100$$

Hausner ratio

It indicates the flow property of the powder and measured by the ratio of tapped density to bulk density

$$\text{Hausner ratio} = \frac{\text{T.D}}{\text{B.D}}$$

Where, T.D= Tapped density, B.D= Bulk density

Table 7.2: Relationship Between Hausner Ratio & Powder Flow

Hausner ratio	Properties
0 -1.11	Free flowing
1.2 -1.6	Cohesive powder

Angle Of Repose / Flow Properties:

Irregular flow of powders from the hopper produces tablets with non uniform weights. As respects content uniformity and dose precision can't be achieved in a production of tablets & capsules. Flow properties depend on particle size shape porosity and density of bulk powder. The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan Q = \frac{h}{r}$$

Where, h = height of pile.

r = radius of the base of pile.

Q = angle of repose.

Lower, angle of repose better the flow property through and irregular surface of the particles give higher angle of repose. It can be decreased by addition of lubricants, of low concentration decreases the angle of repose at high concentration; enhances angle of repose.

Method: A glass funnel is held in place with a clamp on ring support over a glass plate, powder (weighed) and poured in funnel keeping the orifice of funnel blocked. When powder is emptied from funnel, angle of heap to horizontal plane is measured with protractor. Highest

of pile (h) and radius of the base (r) is measured with ruler. Thus the angle of repose is measured.

Compatibility Studies:

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation determined by using suitable analytical techniques like HPLC, FTIR, DSC or DTA.

Procedure:

Drug is mixed with excipients in different ratio. These mixtures were kept in a 5ml glass white colored vials and packed properly. These vials are exposed to $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / 75% $\pm$ 5% RH. 15gm of blend is prepared which is filled in 3 vials. Observations for physical appearance are made at zero weeks, 2 week, and 4week, the samples were withdrawn for analysis of following parameter by KFC Method and HPLC

1. Moisture content
2. Assay
3. Related Substances
4. Appearance.

The compatibilities were carried out to study the possible interactions between the active pharmaceutical ingredients and several inactive ingredients used in the formulations physical mixtures were kept in 40°C / 75% RH and 60°C in a 2ml glass vial in exposed condition for 1 month, excipients are mixed with drug.

ER Coating For The Drug Loaded Pellets:

Preparation of Coating Solution:

Pass the Isopropyl Alcohol through #200 Nylon cloth into the container. Dissolve, half quantity of the Ethyl cellulose in IPA with continuous stirring. Dissolve the PEG 6000 in purified water with continuous stirring in a separate container. Mix the above prepare

Magnesium Stearate and PEG 6000 solution to Ethyl cellulose, continue this stirring for 15 min. After stirring, filter the solution through #200 nylon cloth into separate containers.

Coating Process:

Load the drug coated pellets into the product bowl and carry out the operation as Pre Standard Operating Procedures. Set the inlet temperature to 45°- 60°c & maintain the bed temperature between 38°- 44°c by adjusting the inlet set temperature. Coat the drug pellets by bottom spray Wurster at peristaltic pump RPM of 25-100 and atomizing air pressure of 3.0-5.0 Kg/cm² till the coating solution is completed. After completion of solution, dry the pellets in FBC for about 15 minutes at given bed temperature & Atomization air pressure 3.0kgs/cm². Collect the coated pellets in the containers.

Sifting:

Sift the Ethyl cellulose coated pellets through #16 and collect pellets and store below 25°c.

Packaging And Storage:

Collect sifted Venlafaxine HCl in HDPE Containers lined with virgin double poly bags. Store below 25°C

Procedure:

Standard Preparation:

Transfer 48.0 mg of Venlafaxine Hydrochloride into 25 ml volumetric flask add 10ml of mobile phase sonicate to dissolve. Make up to volume with mobile phase. Transfer the solution through 0.45μ nylon filter paper

Sample Preparation :

Set parameters of dissolution apparatus as mentioned above transfer the six capsules into each individual bowls and operate the apparatus, withdraw 10ml of the

sample solution after 2nd, 4th, 8th, 12th, 18th and 20th hours from each dissolution jar and replace with same volume of dissolution medium at each sampling interval. Immediately

operate the apparatus at the specified speed. Each interval withdraw sample of 10 ml. Filter the solution through 0.45 μ nylon filter paper

RESULTS AND DISCUSSION

Results And Discussion

In the present work Capsule dosage form containing Venlafaxine hydrochloride ER coated pellets were prepared by using Drug layering solution method in pelletization technique and used for the treatment of Depression.

Preformulation

Preformulation data are vital for decision making on the choice of dosage form and excipients and essential for preceding it further for the development of dosage form.

Characterization Of Active Pharmaceutical Ingredient And Polymer

Drug (Venlafaxine hydrochloride), polymers (Ethyl cellulose N50), (Eudragit and surelease) were characterized by using Fourier Transform Infra Red Spectroscopy.

Venlafaxine hydrochloride was analyzed under IR spectra and their results were produced in following figures. The mixture of API with Ethyl cellulose, API with Eudragit, API with Surelease, and their mixture were characterized through IR spectrum and their spectra were given in following figure. The resulted IR spectra were interpreted and presented. The results match the test sample when compared with reference standard.

Table :8.1: Interpretation of IR Spectrum For Venlafaxine Hydrochloride

S.NO	Functional group	Wave number cm ⁻¹
1	CH Stretching (Aromatic)	3014.19
2	CH Streching (Aliphatic)	2936.09
4	C=C	1614.13
5	C-N Stretching	1513.85

6 C-O 1437.67

Venlafaxine hydrochloride showed a prominent IR absorption band in the region of 3014.19 cm^{-1} at CH stretching(Aromatic), a very sharp peak observed at 2936.09 cm^{-1} due to –CH Streching (Aliphatic), at 1614.13 cm^{-1} the absorption was due to C=C, at 1513.85 cm^{-1} due to C-NH was observed, at 3350.71 cm^{-1} the absorption was due to OH, at 1437.67 cm^{-1} the absorbtion was due to C-O. The absorption peak of chlorine occurred at 624.96, 750.33 cm^{-1} .

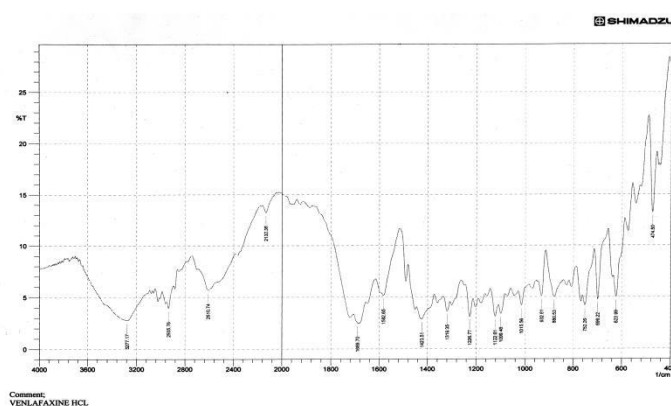


Figure:8.2: FT-IR Spectrum of Venlafaxine Hcl

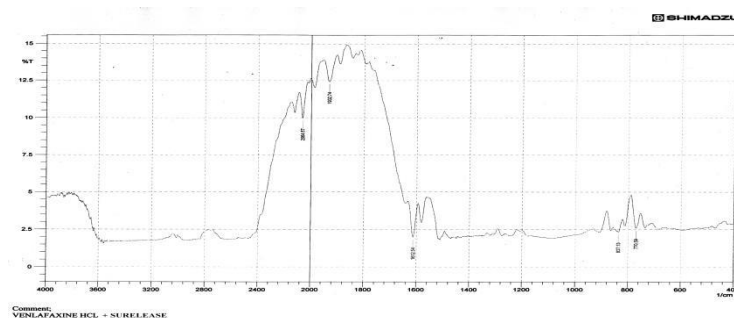


Figure:8.4.FT-IR Spectrum of Venlafaxine Hcl with Spectrum

Thermal Analysis For Characterizing Interaction Between Drug And Excipients

Differential scanning calorimetry was done for the crude drug and its mixture with excipients. The resulted spectra with their melting points were given in figure below. DSC results indicates no presence of interactions between the drug and excipients.

In-Vitro Dissolution for ER Coated Capsules (F4-F11)

The dissolution study was carried out in USP Type II dissolution apparatus. The samples were subjected to Buffer medium with pH 6.8 phosphate for twenty hours. The samples were collected and checked for absorbance through HPLC.

The results were interpreted by plotting the graph with cumulative percentage drug release versus time in hours in graphs.

Formulation F4 SR coated pellets with 5% w/v of Eudragit (independent) produced 91.1% of release in buffer medium and also it is in continued with indiscriminate medium. So, the formulation F5 was coated with 10% Eudragit and this coating results in fast drug releasing within 10 hours in buffer medium. By observing the previous trails, than decided to take pH dependent polymer like Eudragit L100 as it is soluble in pH 6-7, as we have our official medium is also with in this range. In the formulation F6, 95.8% of drug released, the result was improved when compared with F4 & F5. But in this trail the polymer has changed because as our reference product shows pH independent release profile so that, we decided to the use of pH independent polymer. Hence formulation F7 was tried with 3.13% of surelease as SR coating polymer and the acquired result was 83.1% of Venlafaxine HCL release. As above results were not satisfactory, surelease retarding the release of Venlafaxine HCL in Buffer medium when compared with the other formulation. So, the alternate SR coating polymer Ethylcelluolse was decided to apply in the further formulation.

Formulation F8 was coated with 9.0% of surelease to the core pellets and the result was obtained as 96.6%. To retard the drug release more than the formulation F7 the concentration of surelease has been increased. To retard the drug release with ethylcelluolse the concentration was decided to take equal to (or) less than the concentration of surelease. Hence, formulation F9 & F10 was tried with 5.13% & 7.13% and Venlafaxine HCL was released and observed desired range in phosphate buffer & the optimized batch was taken with ethylcelluolse.

From the above observation, formulation F4 to F7 does not complies with desired drug retard in the phosphate dissolution medium and the continuous buffer stage dissolution was performed but not satisfactory. Formulation F8 and F9 had a better drug retarding property so the process was carried to next continuous pH 6.8 phosphate buffer stage for 20

hours. F9 & F10 showed the good sustained characters when compared with the F4 to F7. But the formulation F11 showed good release data.

When compared to F10, formulation F 11 has shown good release tendency like the reference product. Finally by observing the release profile of both F10 & F11 both these trails were taken for the indiscriminate medium analysis.

Dissolution profile of ER Coated Pellets with Reference product Formulations (F4-F11)

S.No	Time in hrs	Percentage Drug Release								
		Effexor 75mg	F4	F5	F6	F7	F8	F9	F10	F11
1	0	0	0	0	0	0	0	0	0	0
2	2	14.2	13.6	33.6	11.2	10.2	22.3	19.5	12.6	10.2
3	6	42.6	22.7	55.3	39	21.2	42	35	23.6	24.9
4	8	60.2	46.9	75.6	55	32.1	56.9	52.35	47.8	33.5
5	10	73.7	67.6	86.4	73.2	60.3	72.6	70.45	68.3	62.9
6	12	81.4	76.1	98.9	82.6	69.6	79.7	78.9	78.1	79.8
7	18	90.4	81.3	ND	90.6	76	87.4	85.3	83.2	85.5
8	20	97.8	91.1	ND	95.8	83.1	96.6	95.3	94	96.2

Formulation F4- F11 was designed by SR coating the core pellets of optimized formulation different SR coating polymers such as Surelease, Ethylcellulose and Eudragits. The micromeritic properties such as bulk density, tapped density, angle of repose, hausner's ratio, and Compressibility index were studied. The overall results were tabulated in table no:

The angle of repose for the formulations F4-F11 ranges from 32.6° – 29.87° which depicts excellent flow character. Bulk density ranges from 0.628 gm/ml-0.66gm/ml. Tapped density for the enteric coated formulations F4-F11 lies between 0.778gm/ml-0.703 gm/ml.

Hausner's ratio for enteric coated pellet formulations (F4-F11) ranges from 1.23gm/ml-1.06 m/ml .The values shows the property of excellent flow character. Percentage of Compressibility index for the formulations F4-F11 was found to be 19.2, 14.6, 13.7, 13.06, 11.7, 11.5, 11.1 and 6.11 respectively. These values demonstrates the excellent flow character of formulations F4-F11

CONCLUSION

- The active pharmaceutical ingredient Venlafaxine Hydrochloride was subjected to preformulation study, which encompasses the “Accelerated drug excipient compatibility study”, and the results obtained with selected excipients showed good compatibility with Venlafaxine Hydrochloride drug.
- Venlafaxine Hydrochloride coated pellets were formulated by using commercially available sugar pellets and Venlafaxine Hydrochloride SR coated capsules were filled by automatic capsule filling machine with various excipients used during formulation . The optimization procedures aided in the stabilization of the formula and in the formulation of the Venlafaxine Hydrochloride modified release capsules.
- The stability of the capsules and pellet was determined by conducting “Accelerated stability testing” in $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\%\text{RH}$ and $25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \text{RH} \pm 5\% \text{RH}$, $30^{\circ}\text{C} \pm 2^{\circ}\text{C} / 65 \pm 5\% \text{RH}$ conditions for 3 months as per ICH guidelines in HDPE containers. Finally after the duration, the product was analyzed for weight variation, content uniformity, assay and dissolution studies. By the stability studies, the formulated Venlafaxine Hydrochloride modified release capsules and pellets proved to be stable throughout the period of the storage.
- The Venlafaxine Hydrochloride Sustained release pellets were loaded in size 1 hard gelatin capsules. It showed good results in formulation of stable dosage. The dissolution profile of the prepared Venlafaxine Hydrochloride sustained release capsules were compared with that Venlafaxine Hydrochloride modified release capsules (Effexor SR) of the product. The

release was found similar to that of innovator. So the prepared product was said to be equivalent with innovator.

- When come to discussion of dosage form SR coated pellets in capsule showed better drug release. Sustained release pellets have minimum volume in size, greater surface area and more surface activity. The area of the drug loaded pellets release rate was also more. Because of Small size, pellets enter into the systemic circulation in very fast. Moreover there was no accumulation of drug in the body. Drug release rate was more.
- The release in the starting hours is controlled by increasing the concentration of Ethyl cellulose N-50 in the formulations in F10 formula and the plasticizer is also increased. It was observed that the release profile of the pellets were good by using ethyl cellulose polymer, when compared with the Eudragit's (independent), Eudragit's (dependent) L100 & Surelease.
- Finally I conclude that Sustained release pellets of formulation F11 has relevant drug release rate than Surelease, Polyacrylates and it has better stability, Bioavailability.

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