PHYSICOCHEMICAL CHARACTERIZATION OF VENLAFAXINE HYDROCHLORIDE FOR FAST-DISSOLVING FORMULATION DESIGN

Sarika Gupta [1], Abdul Wadood Siddiqui [2]*, Pravin Gupta [3], Dinesh Kumar Sharma[4]

[1]*Department of Pharmacy, Institute of Biomedical Education and Research, Mangalayatan University, Aligarh-202146, India*
[2*] *School of Pharmacy, Mangalayatan University, Aligarh-202146, India*
[3]*Shakuntala Devi College of Pharmacy, Kakyoli Nawabganj, Farrukhabad-209501, India*
[4]*Institute of Applied Sciences, Mangalayatan University, Aligarh-202146, India*

*Corresponding Author Email ID: abdul.siddiqui@mangalayatan.edu.in, sarikagupta7017@gmail.com

KEYWORDS

Venlafaxine HCl, UV studies, FTIR, Partition coefficient, DSC.

ABSTRACT

Objective: The study focuses on the characterization of Venlafaxine Hydrochloride through a series of physicochemical evaluations to ensure its suitability for pharmaceutical development.

Experimentation: Organoleptic properties such as color, odor, and appearance were assessed. The melting point was determined using a capillary method with an average value calculated from three trials. UV spectrophotometric analysis in ethanol was performed to identify the maximum absorbance wavelength. A standard curve of calibration was plotted using absorbance values from prepared dilutions (5–30 µg/mL). Solubility studies were conducted distilled water and in various solvents (methanol, ethanol, and acetone) as well as phosphate buffer 6.8 pH to evaluate equilibrium solubility, while the distribution coefficient (Kp) was calculated using the shake-flask method with octanol and water to estimate lipophilicity. The pH of a freshly prepared 0.1M solution of Venlafaxine HCl in distilled water was measured. Finally, compatibility with excipients was studied using DSC and FTIR to detect potential chemical interactions.

Result & Discussion: The physicochemical parameters like melting point, λ max, solubility, and partition coefficient were found to be 217±0.08 ^{O}C, 224.8 nm, 401±0.45 mg/ml, and 395 mg/ml. 25 mg/ml, 0.8 mg/ml and 23 mg/ml respectively. The pH of Venlafaxine HCl was found to be 6.8. From the FTIR & DSC spectra, since all of the drug's distinctive peaks were preserved, it is evident that the drug and excipients are compatible. Therefore, the API and these excipients are not incompatible.

Conclusion: This comprehensive characterization provides foundational data for fast dissolving formulation design and stability evaluation of Venlafaxine HCl.

INTRODUCTION

Physico-chemical properties of the of pharmaceutical compounds both on their own and in mix with excipients is described as a preformulation study [1]. The first stage in the rational development of various dosage forms for an active pharmaceutical ingredient is preformulation research [2]. The most common indications of degradation in an active pharmaceutical ingredient (API) include changes in colour, taste, odour, polymorphic structure, and crystallization, while oxidation, and reduction which are generally associated with pharmaceutical incompatibility. These changes are typically the result of chemical interactions with excipients [3].

Adverse drug-drug and drug-excipient combinations can cause interactions that can lead to chemical, physical, and therapeutic instability. Changes in a drug's organoleptic qualities, such

as appearance, color, form, odor, taste, etc., that do not involve the formation of chemical bonds or the breaking of the drug's structure are referred to as physical instability. Changes in the chemical structure of a drug molecule that lead to drug breakdown, decreased drug content, and the production of other molecules, such as degradation products, are referred to as chemical instability. Chemical and physical instability can also raise safety issues. [4]. This study aims to determine some of the physiochemical properties such as pH, solubility, partition coefficient, melting point, lambda max, infra-red spectra and DSC spectra etc [5]. One of the most crucial and significant aspects of API that affects their bioavailability is their solubility [6].

Venlafaxine is a bicyclic phenylethylamine compound that comes under the category of antidepressant. It acts by blocking transport proteins and preventing their presynaptic reuptake, it raises serotonin, norepinephrine, and dopamine levels in the brain. Consequently, more transmitters are available at the synapse, which subsequently stimulates postsynaptic receptors. Serotonin reuptake inhibitors (SNRIs) interact primarily with serotonergic and noradrenergic neurons, while cholinergic and histaminergic receptors are little affected or unaffected by SNRIs [7]. In comparison to norepinephrine reuptake inhibitors, A stronger inhibitor of serotonin reuptake is venlafaxine HCl. With a dose of 25-75 mg, Inhibition of serotonin reuptake is the primary action of venlafaxine. The higher the dosage, the greater the effect on the norepinephrine transporter as well [8].

This physicochemical investigation was done by selecting the excipients that are used in fast-dissolving formulations for example fast dissolving tablets and films etc.

MATERIALS

Venlafaxine HCl, received from Akums Drugs & Pharmaceuticals Ltd, Haridwar, Ethanol, Changshu Hongsheng Fine Chemical Co. Ltd. Excipients like Sodium carboxy methyl cellulose & Sodium alginate (Polymers), sodium starch glycolate (Super-disintegrant), mannitol (Sweetening agent) was obtained from CDH and Propylene glycol (Plasticizer) from Fisher Scientific Ltd. Every chemical was of analytical quality.
The instruments such as an electronic balance, Double beam UV-Vis Spectrophotometer, FT-IR Spectrophotometer, and Differential Scanning Colorimetry were used.

METHODS

Organoleptic Characteristics

The organoleptic characteristics such as color, odor, taste, etc. were visually checked for venlafaxine HCl API.

Determination of melting point

Venlafaxine HCl's melting point was predicted by placing a tiny quantity of the drug in a capillary tube that was closed on one end. The temperature at which the drug melted was measured by placing the capillary tube in a melting point instrument. This was done three times, and the average result was recorded [9].

Solubility

Venlafaxine HCl's solubility was determined by taking an excess amount of API and dissolved in distilled water, various organic solvents (methanol, ethanol, acetone) and phosphate buffer 6.8 pH separately up to its saturation and subjected to mechanical shaking at 100 rpm for 24 h

at room temperature in order to achieve equilibrium. By measuring absorbance at 224.8 nm, the amount of venlafaxine HCl in the filtrate was ascertained. [10].

Distribution Co-efficient

In a separating funnel, 5 ml of octanol-1 was combined with 5 ml of distilled water and a known amount of venlafaxine HCl. Next, using the shake flask method, two phases were allowed to equilibrate for 24 hours at 37 ºC while being shaken intermittently. Following the required dilution, the UV spectroscopic approach was used to estimate the drug's concentration in both the organic and aqueous phases. The following formula was used to determine the apparent distribution coefficient (Kp), which is the ratio of drug concentration in each phase:

$$K_P = \frac{Corg}{Caq}$$

Where, Caq, Corg are the drug's concentration in the aqueous phase and in the organic phase respectively [11].

pH Determination

A pH meter was used to measure the freshly manufactured Venlafaxine HCl 0.1M solution in distilled water [12].

Standard Curve of Venlafaxine HCl

The first Stock solution of venlafaxine hydrochloride was made by dissolving 10 mg in 100 ml buffer of distilled water. It was estimated that the conc. of prepared stock 1 solution was 100 µg /ml. The First stock solution was diluted further to get a conc. of 10 µg /ml. The 400–200 nm range was used to scan the solution using distilled water as blank by double beam spectrophotometer. Preparation of dilution of 5-30 µg/ml, the absorbance of made dilutions was evaluated at λmax 224.8 nm. After that, the linearity curve was produced using the x-axis for concentration and the y-axis for absorbance [13].

COMPATIBILITY STUDIES

Physical mixes of the drug and excipients at a 1:1 w/w ratio are used in compatibility screening experiments. The samples are often equilibrated under a variety of stress conditions, such as high temperatures, which might hasten the drug-excipient interactions. To find the physical incompatibility, these samples are visually inspected for any color changes or powder mixture agglomeration. Additionally, thermoanalytical and spectroscopic methods are used to examine the physical mixtures for chemical incompatibility [14].

FT-IR Spectroscopy

FTIR spectrophotometer (BRUKER/ALPHA ATR, Germany) was used to identify chemical interactions by observing changes in peaks of functional groups. The drug was mixed with potassium bromide in 1:99 proportion by triturating into disks in a hydraulic press after triturating with potassium bromide in a glass crusher and pestle and the FTIR Spectrum was recorded between 400-4000 cm-1 with IR solution software by KBr Disc method. Potassium bromide was used as a blank while running the spectrum [15,16].

Differential scanning calorimetry

DSC (PERKIN ELMER/DSC 4000, Netherland) was used for the determination of changes observed in drug sample and drug & polymer mixture (Venlafaxine HCl and drug: polymer physical mixture). Samples (2-4 mg) were sealed in aluminium cells, and DSC apparatus was set between 25°C and 300°C in a nitrogen environment at a constant rate of 10°C/min. An empty alumina pan served as the standard [17,18].

RESULTS AND DISCUSSIONS

Organoleptic Characteristics

The organoleptic characteristics such as color, odor, appearance, and nature of the drug venlafaxine HCl were checked.

Table 1: Organoleptic test of Venlafaxine HCl

Venlafaxine HCl		
S. No.	**Parameter**	**Observed Value**
a.	Odor	No odor
b.	Colour	White
c.	Appearance	Crystalline
d.	Nature of the drug	Solid

Melting Point

It was determined by using the capillary method and found to be 217ºC in an average with three replicates which was compared to that found in the literature in the range of 215 to 217ºC. The obtained melting point is near the standards obtained from the literature. This confirms the purity of the obtained venlafaxine HCl sample.

Table 2: venlafaxine HCl's melting point value

Drug	**Results**		
Venlafaxine HCl	**Practical**	**Average**	**Standard**
	216 ºC	217 ºC	215 to 217ºC
	217 ºC		
	218 ºC		

Saturation solubility

The saturation solubility of the venlafaxine HCl was studied in distilled water, methanol, ethanol and the phosphate buffer solutions of pH 6.8, and acetone. The data compiled after 48 hrs. is given in the below table 3. As a result, obtained the venlafaxine HCl was found to have limited solubility in. The highest solubility was found in distilled water.

Table 3: Saturation solubility of Venlafaxine HCl

S. No.	**Drug**	**Vehicles**	**Saturation Solubility**	**Results**
1.		Water	401 mg/ml	Freely soluble
2.		Methanol	395 mg/ml	Freely soluble

3.	Venlafaxine HCl	Ethanol	25 mg/ml	Soluble
4.		Phosphate buffer (pH 6.8)	23 mg/ml	Soluble
5.		Acetone	0.8 mg/ml	Slightly soluble

The study reveals that venlafaxine HCl exhibits the highest solubility in the distilled water as compared to other solvents. Thus, distilled water was chosen for the preparation of the calibration curve.

Partition Coefficient & pH

Table 4: Partition coefficient and pH value of Venlafaxine HCl

S. No.	Parameter	Reported value	Observed Value
3.	Partition Coefficient	1-3	1.09
4.	pH	6-7	6.8

Standard Calibration Curve

The λmax of venlafaxine HCl was determined by UV-Vis spectrophotometer. The distilled water was used for the determination of the calibration curve. The λmax was found to be 224.8 nm (Figure 8) which is closer to that of the standard λmax which is 224-227 nm.
The calibration curve of the venlafaxine HCl was determined by using UV-Vis spectrophotometer via a fixed wavelength measurement option. The calibration curve obtained were following Beer's Lambert's law. The calibration curve obtained from using water has an R^2 value of 0.9949.

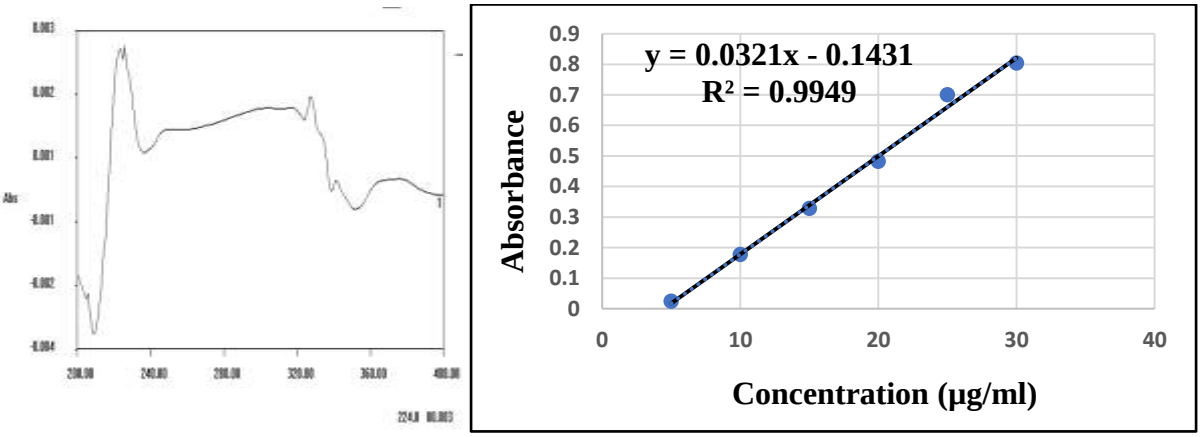


Fig. 1 UV Spectra and a standard curve of Venlafaxine HCl

DRUG-EXCIPIENTS INCOMPATIBILITY STUDIES

Fourier transform infrared spectroscopy

The compatibility of Venlafaxine HCl with excipients was investigated using FTIR spectroscopy. The primary functional groups of the molecule are aliphatic alcohol, tertiary amine, and aromatic ether, according to the Venlafaxine HCl spectrum. The peak that was most intense seen at 1244 cm-1 due to C-N stretching in the Venlafaxine HCl structure. Second sharp peak was observed at 2900 cm-1. which indicated the presence of Cycloalkane, peak at 3347

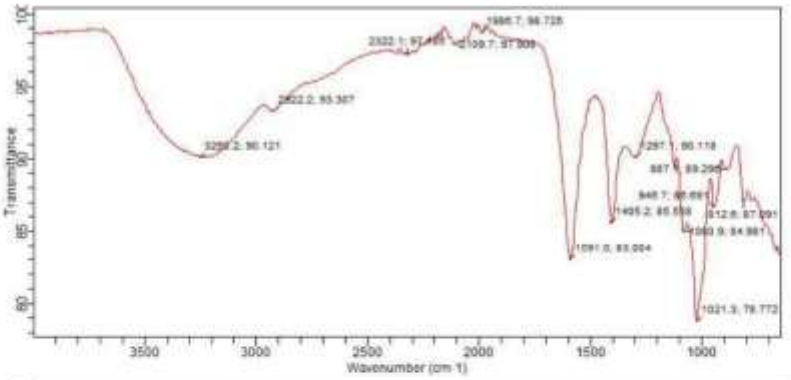
cm-1 was due to O-H stretching. A peak at 1244 cm-1 indicates the presence of C-N stretch of 3^0 Amine seen in Fig. 2(a). From the FTIR spectra as seen in Fig. 2(b), (c), (d), (e), (f), (g) Since all of the drug's distinctive peaks were preserved, it is evident that the drug is compatible with sodium alginate and other excipients. Therefore, the drug and these excipients are compatible.

Table 5: Interpretation of FTIR spectrum of venlafaxine HCl

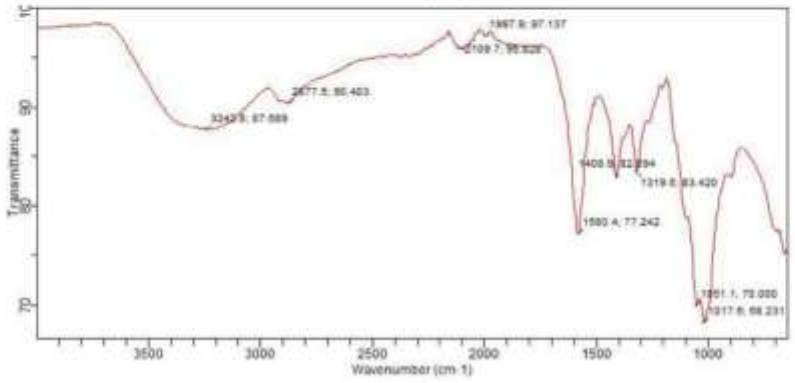
Functional Group	**Wave number (cm^{-1}) detected**	**Bond Type**
Tertiary Amine	1244.9	C-N Stretch
Cycloalkane	2933.4	C-H Stretch
Aliphatic Alcohol	3347.1	O-H Stretch
Aromatic Ether	1177.8	C-O Stretch

Table 6: Interpretation of FTIR spectrum with Excipients

Bond Type	**Peaks obtained Wave number (cm^{-1})**				
	Venlafaxine HCl	Ven.+ Sod. Alginate	Ven.+ Sod. CMC	Ven.+ Sod. Alginate + SSG + Mannitol	Ven.+ Sod. CMC+ SSG + Mannitol
C-N Stretch	1244.9	1244.9	1274.7	1245.7	1248.9
C-H Stretch	2933.4	2933.4	2933.4	2933.8	2932.5
O-H Stretch	3347.1	3347.1	3347.1	3347.1	3316.7
C-O Stretch	1177.8	1177.8	1107.1	1180.3	1182.9


Transmittance
Wavenumber (cm-1)
3500
3000
2500
2000
1500
1000

a


Transmittance
Wavenumber (cm-1)
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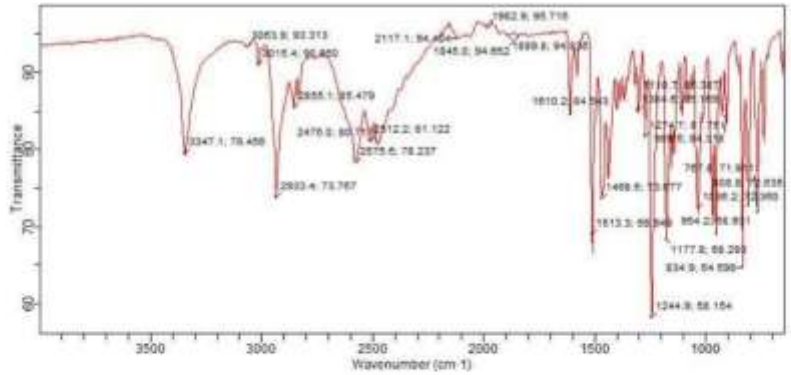
3000
2500
2000
1500
1000

b


Transmittance
Wavenumber (cm-1)
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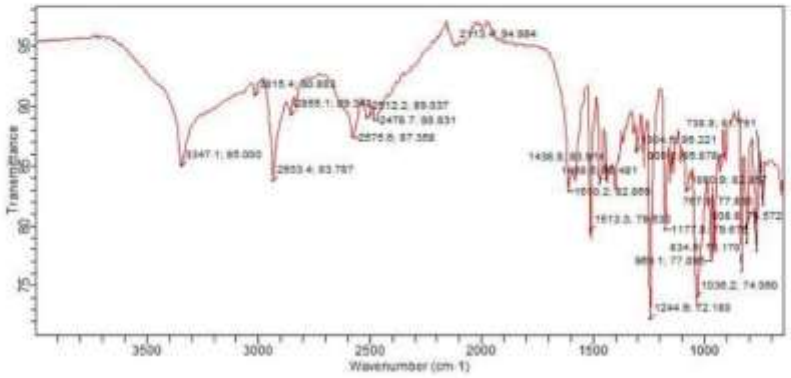
3000
2500
2000
1500
1000

c


Transmittance
Wavenumber (cm-1)
3500
3000
2500
2000
1500
1000

d

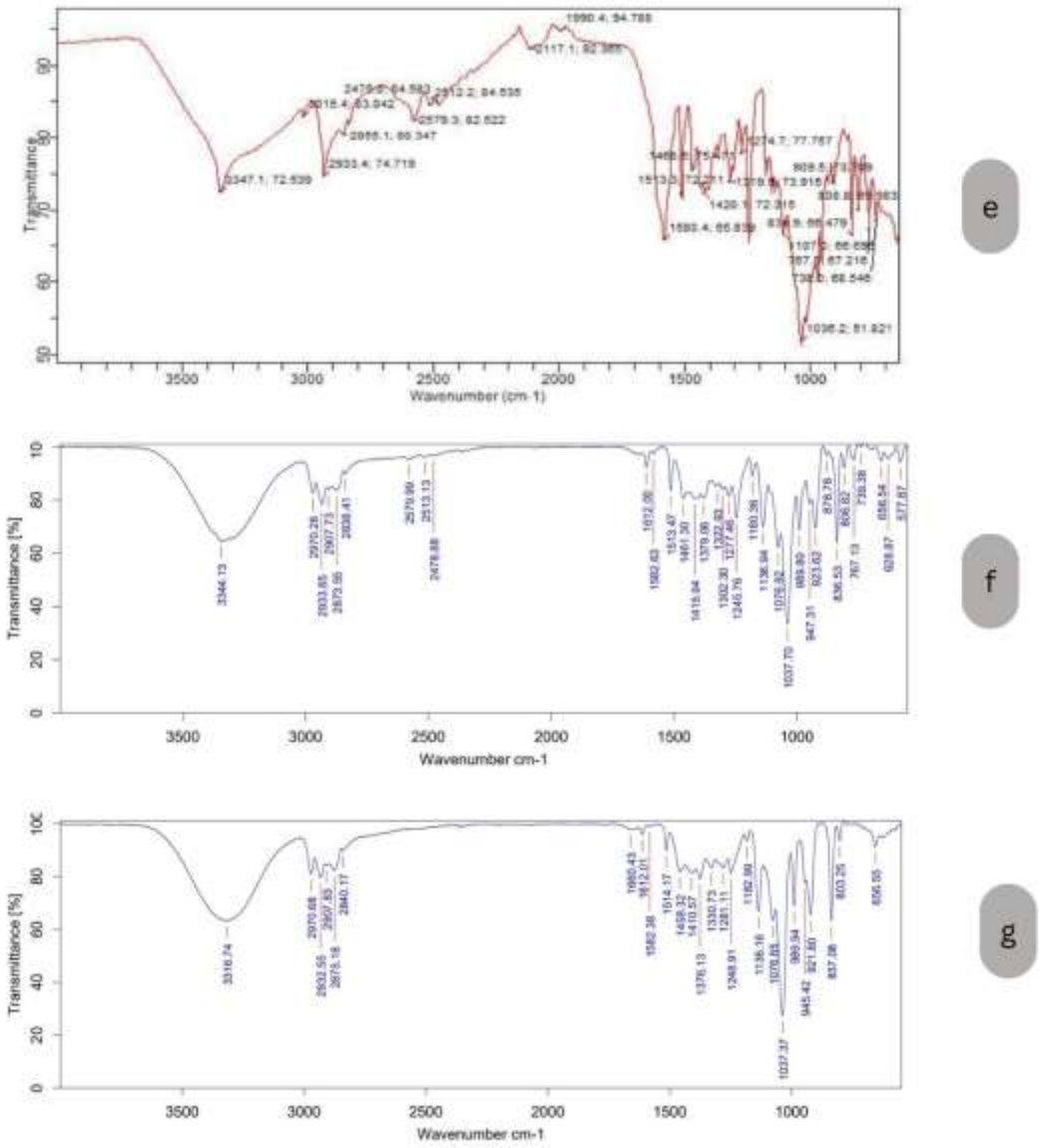


Fig.2(a) FT-IR spectra of Venlafaxine HC(D). (b) FT-IR spectra of Sodium Alginate. (c) FT-IR spectra of Sodium CMC. (d) Mixture of D and Sodium Alginate. (e) Mixture of D and Sodium CMC. (f) Mixture of D, Sodium Alginate, Propylene Glycol, SSG & Mannitol. (g) Mixture of D, Sodium CMC, Propylene Glycol, SSG & Mannitol.

Differential Scanning Calorimetry (DSC)

The DSC graph of the Venlafaxine HCl API was obtained to know the melting point. The DSC graph showing the peak of the melting point is given in Figure 3 & 4. The DSC graph has a peak at 211ºC indicating the melting point of the Venlafaxine HCl API. The thermogram does not show any other peak other than that of melting point at 211ºC. This indicates that the drug is in pure form and the DSC graph has a peak at 165 ºC and 163 ºC indicating the melting point of the Venlafaxine HCl API in a mixture with sodium alginate and sodium carboxy methyl cellulose polymers respectively.

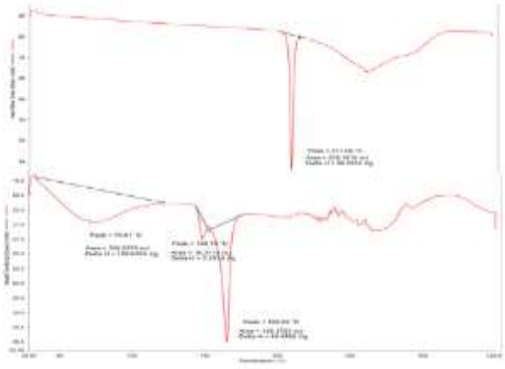


Figure 3: DSC spectra of Venlafaxine HCl (A) and Venlafaxine HCl + Sodium alginate (B)

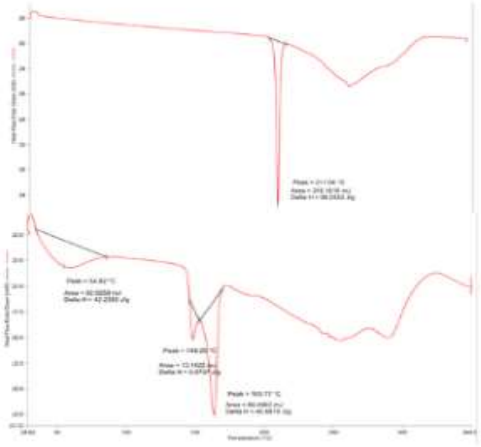


Figure 4: DSC spectra of Venlafaxine HCl (A) and Venlafaxine HCl + Sodium carboxy methyl cellulose (B)

SUMMARY

Determining the features of the medication that will enable a precise risk assessment throughout development depends heavily on the preformulation phase. It often starts in the optimization stage, lasts through predomination, and then enters the early stages of development. Therefore, preformulation must be carried out as carefully as possible to enable making logical conclusions. The goal of the Venlafaxine API preformulation project is to produce results that will help create stable and bioavailable fast-dissolving dosage forms.

ACKNOWLEDGEMENT

I have gratitude to Akums Drugs & Pharmaceuticals Ltd. Haridwar for providing me drug as a gift sample. I am also thankful to Diya Labs Pvt. Ltd, Mumbai. for his help in performing the FTIR and DSC experiment. I am thankful to Mangalayatan University, Aligarh for providing the chemicals and instruments required for the experiment.

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