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Original Article

FORMULATION AND EVALUATION OF MATRIX TABLET OF VENLAFAXINE HCL BY USING DIRECTLY COMPRESSIBLE CO-PROCESSED EXCIPIENT

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ABSTRACT

Objective: The sustained release of drug from the dosage form is useful especially for achieving controlled plasma level of the drug as well as improving bioavailability. The objective of the present work was to release matrix tablet of Venlafaxine HCl by using directly compressible co-processed Excipient.

Methods: Co-processed excipient (Chitosan 88%: eudragit s-100) was prepared in the ratio of 1:1, 1:3, and 1:5 by the solvent evaporation method. The sustained release matrix tablets were prepared by using Co-processed excipient by direct compression and formulate formulations such as F1to F9. The tablets evaluated for various physical parameters. Direct compression method followed by optimization of the evaluation parameters was employed to get the final optimized formulation.

Results: The developed Co-processed excipient was characterized for DSC, FTIR, SEM and XRD which confirm the absence of any chemical changes during co-processing. Co-processed excipient prepared in the ratio of 1:5 showed excellent flow properties. Among all formulations, Optimized formulation F9 showed the desired release profile 98.7% for a period of 24 h in phosphate buffer (pH 7.4). The release co-efficient values 'n' (>0.5) indicated that the drug release followed non fickian anomalous mechanism based on formulation factors. Developed formulations were kept for stability study for three month as per ICH guidelines and found to be stable

Conclusion: Developed co-processed excipient showed good drug release retarding property and could be alternate way to overcome the problems associated with single polymer alone. Venlafaxine HCl matrices could be developed with desirable release modulation for a once daily administration.

Keyword: Co-processed excipient, Sustained release, Matrix tablet, Chitosan 88%, Eudragit s-100, Venlafaxine Hydrochloride.

INTRODUCTION

In recent time, excipients are the largest components of any pharmaceutical formulation [1]. The International Pharmaceutical Excipients Council defines excipients are the substances which present in a finished pharmaceutical dosage form other than the active drug substance [2-3]. Excipients have been appropriately evaluated for safety and are included in a drug delivery system to aid the processing of the drug delivery system during its manufacture, enhance stability, bioavailability, and patient acceptability or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or optimal use and having multifunctional property are provide pharmaceutical manufacturers with cost saving drug development and help in drug formulations innovation[4].

Now a day, most of the pharmaceutical manufacturing industries opting for direct compression tableting as it requires fewer processing steps, simplified validation, elimination of heat and moisture, economy, and improved drug stability compared with wet granulation technique. The term 'direct compression' (DC) is the process by which tablets are prepared directly from the powder blends of active ingredients and suitable excipients. For direct compression its prerequisite that excipient used for formulation should have good flow and compression property [5].

Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, that leads to the formation of excipients that granulates with superior properties compared with physical mixtures of components or individual components.[6] Usually acombination of plastic and brittle materials is used for co-processing. This combination prevents storage of too much elastic energy during the compression, which results in a small amount of stress relaxation and a reduced tendency of capping and lamination thereby optimum tableting performance. [6] The objective of co-processing is to provide a synergy of functionality improvements, also having superior intrinsic performance high compatibility, high intrinsic flow, good lubricating efficiency, improved blending properties and good binding properties [7].

Chitosan is a cationic polyamine with a high charge density at pH< 6.5; and so adheres to negatively charged surface and chelates metal ions [8]. It is a linear polyelectrolyte with reactive hydroxyl group. [9] The properties of chitosan relate to its polyelectrolyte and polymeric carbohydrate character. The presence of the number of amino groups allows chitosan to react chemically with anionic system, which results in alteration of physicochemical characteristics of such combinations. The major pharmaceutical applications of chitosan in pharmaceutical formulations for drug delivery applications have been investigated in numerous studies. These include, Controlled drug delivery application, Rapid release dosage forms, improved peptide delivery, Colonic drug delivery system [10].

Eudragit S-100 are anionic Polymethaacrylates are known worldwide in the industry under the trade name Eudragit. These polymers allow the active in solid dosage form to perform during the passage of the human body. The flexibility to combine the different polymers enables to achieve the desired drug release profile by releasing the drug at the right place and at the right time and, if necessary, over a desired period of time. Other important functions are protection from external influences. The ratio of the free carboxyl groups to the ester groups is approx. 1:2 in. Eudragit S-100 used as an enteric coating film former for solid-dosage forms [11].

Venlafaxine HCl is a novel third generation antidepressant drug with a bicyclic structure different from tricyclic, tetracyclic, or other commercially available antidepressants. It is a white crystalline solid, soluble in water (534 mg/mL). The dose of venlafaxine ranges from 75 to 350 mg/day. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV) were proved to have improved efficacy, faster speed of onset of effect, and greater safety in the treatment of

depression, generalized anxiety disorder, and social anxiety disorder in adults compared with previous medicines, such as the selective serotonin reuptake inhibitors Venlafaxine works effectively against a broad range of depressive conditions, both mild to moderate and severe, whether occurring in in-patients or out-patients. However, due to the short steady state elimination half-life (3–4 h for Venlafaxine and 10 h for ODV), the drug has to be administered 2 or 3 times daily so as to maintain adequate plasma levels of drug. Once a daily sustained release formulation developed for increasing patient compliance and convenience as well as a superior benefit/ risk ratio [13]. Thus, this work focused on the formulation and evaluation of matrix tablet of venlafaxine HCl by using directly compressible co-processed excipient comprising of Chitosan 88% deacylated and Eudragit S-100 by the solvent evaporation method.

MATERIALS AND METHODS

Materials

Venlafaxine HCl was obtained as a gift sample from Orchid Chemicals And Pharmaceuticals Ltd, Aurangabad, India. Chitosan (88% deacylated) supplied by Everest Biotech Bengaluru., Eudragit S- 100 Evonik Degussa, Mumbai, India Pvt. Ltd., and Polyvinylpyrrolidone (K-30) was received as gift from Alkem laboratory Ltd., Mumbai. Also microcrystalline cellulose, magnesium stearate, Talc. All other excipients and chemicals used were of analytical grade (AR).

Methods

Preparation of directly compressible Co-processed Excipient

The Co-processed excipient of Chitosan (88% deacylated) and Eudragit s-100 was prepared by using the solvent evaporation method. Chitosan 1 gm was accurately weighed and dissolved in 15 mL of 3% v/v acetic acid solution . Similarly, Eudragit S- 100 (5 gm) was separately dissolved in 7 mL ethanol and was covered to prevent evaporation. This dispersion was slowly added with stirring to the Chitosan solution. The mixture was poured in a Petri plate and was dried at 50°C for 48 h. co-processed excipient containing 1:1, 1 : 3,and 1: 5 ratios of chitosan: Eudragit S- 100 were prepared using this method. The dried co-processed excipient was stored in a desiccator until used [14].

Characterization of co-processed excipient

Fourier transforms infrared spectroscopy (FTIR)

Co-processed excipient discs were prepared by pressing the Co-processed excipient with potassium bromide and the spectra between 4000to 400 $cm^{-1}$was recorded using FTIR spectrophotometer (SHIMADZU 84500 S, Tokyo, Japan)[15].

Differential scanning calorimetry (DSC)

DSC analysis was performed using Shimadzu-Thermal Analyzer DSC 60 on 2-5 mg sample was taken in the quantity of 2 to 4 mg. Samples were heated in an aluminum pan at a rate of 10°C / min within a 30 to 300°C temperature range under a nitrogen flow of 10 ml/min. An empty sealed pan was used as a reference [16].

X ray Diffractometry (XRD)

Approximately 100 mg of the sample was exposed to Cu radiation wavelength 1.5406 A°, having temperature rang 170 °C to +450 °C in a wide-angle powder X-ray diffract meter (Make/Model-Bruker AXS D8 Advance). The instrument was operated in the step-scan mode, in Max. Use angular range is 3° to 135°.

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) is a method for high resolution surface imaging. The SEM uses an electron beam for surface imaging.(SEM Make JEOL Model JSM - 6390LV) double-sided carbon tape was affixed on aluminum stubs over which the powder sample of Co-processed excipient samples was observed for morphological characterization using a gaseous secondary electron detector.

Powder flow properties of co-processing excipients

The following micromeritic properties of the co-processed excipients were studied.

Bulk and tapped densities

7.5 g of the blend were carefully poured into a 50 ml graduated cylinder. The volume occupied by the blend was read and the bulk density calculated in gm/ml. The cylinder containing the blend was tapped until constant volume was obtained using bulk density apparatus from a height of 2 cm and the tapped density calculated in gm/ml.

Percentage compressibility (Carr's index) and Hausner's ratio

The percentage compressibility (CI) was calculated from the difference between the tapped (Td) and the bulk densities (Bd) divided by the tapped density and the ratio expressed as a percentage. The Hausner's ratio (HR) is the ratio between the tapped and bulk density.

CI= (Tapped density – Bulk density)/ Tapped density× 100

HR= Tapped density/Bulk density

Drug –Excipient compatibility study

FTIR study

To analyze the compatibility of drug with polymers, the infrared spectrum of pure venlafaxine HCl sample and its combination with excipients mixture was recorded using FTIR spectrophotometer (SHIMADZU 84005). The scanning range was 4000 to 400 cm^{-1}. A change in spectrum pattern of drug due to presence of polymers was investigated to identify any chemical interaction [15].

DSC study

The possibility of drug–excipient interaction was further investigated by differential scanning calorimetry (DSC). DSC analysis was performed using Mettler Star SW 9.01 DSC- 60(SHIMADZU). DSC of pure Venlafaxine HCl alone and its combination with excipients mixture was taken in the quantity of 2 to 4 mg sample Samples were heated in an aluminum pan at a rate of 10°C / min within a 30 to 300°C temperature range under a nitrogen flow of 10 ml/min. An empty sealed pan was used as a reference.

Preparation of Matrix tablet of Venlafaxine HCl

Matrix tablets of Venlafaxine HCl, each containing80 mg [15]. Venlafaxine HCl was prepared by using Co-processed excipient by direct compression method. The composition of various formulations was shown in [Table 1]. Polymer composition was selected on the basis of trial taken for the formulated preparation. All the ingredients weighed accurately, passed through 60 mesh and mixed in geometric order. Mixing was continued for 10 min to achieve uniform mixing then the mixture was lubricated with magnesium stearate for 5 min. Different polymers were used alone or in combination to formulate matrix tablet of Venlafaxine HCl. The lubricated blend was then compressed into a tablet using 10 mm standard round shaped punches on 10 station tablet compression machine JM-10 (JAGUAR Co. Pvt. India). Each tablet contains 80 mg of Venlafaxine HCl base and total weight of a tablet was 300 mg depending upon polymer concentration. All the tablet formulations were stored in air tight container till further use.

Evaluation of powder blends

The powder blends were evaluated for flow property (angle of repose), loose bulk density, tapped density, compressibility index and drug content. Angle of repose was determined by fixed funnel method. Loose and tapped density was determined by cylinder method and for Carr's Index (CI) value following equation was used:

Carr's Index = tapped bulk density-loose bulk densityx100/tapped density. Hausner's ratio was also calculated to define the flow property. A Hausner's value between 1.12 to 1.25 is indication of good flow property.

Evaluation of tablets

The prepared tablets were evaluated for their physical parameters like hardness, thickness, weight variation, friability and drug content. For hardness testing Monsanto hardness tester and for

frability Roche friabilator (Campbell Electronics, Mumbai, India) was used to determine the value. Vernier caliper was used to measure the thickness of the tablets. Weight variation was performed as per official method.

Drug Content Estimation

Twenty tablets were selected randomly and the average weight was calculated. Tablets were crushed in a mortar and accurately average weighed amount of tablets triturate was taken for analysis. Samples were transferred to different volumetric flasks and were diluted up to the mark using phosphate buffer (pH 6.8). The content was shaken well and kept for 30 minutes for dissolving the drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ_{max} 225 nm against blank as reference.

***In vitro* dissolution studies**

In vitro drug release study of the samples was carried out using USP – type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml of 1.2 pH HCl buffer (2 hours) and 6.8 pH phosphate buffer (22 hours) for 24 hours, was placed into the dissolution flask maintaining the temperature of 37 ± 0.5^{0}C and rpm of 50. The apparatus was allowed to run for 24 hours. Samples measuring 5 ml were withdrawn after every 1 hour up to 24 hours manually. During sampling, samples were filtered.

The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were analyzed at 225 nm using phosphate buffer (pH 6.8) as blank. The cumulative percent drug release was calculated and the graph was plotted between cumulative percent drug release verses time (h) [20-21].

Kinetic analysis of release data

To describe the kinetics and percent releases of the drug release from sustained release matrix Venlafaxine HCl formulation (trial batches). The drug release data from trial batches were fitted in to various kinetic release mathematical models such as zero order, first order, Higuchi, Korsmeyer-Peppas models by using PCP-Disso-v3 software. The regression coefficient (r^2) value compared to each other and selected best fit model, the release mechanism of matrix tablet formulation from system was decided from release exponent value.

Table 1: Composition of formulations of matrix tablet of Venlafaxine HCl

Ingredients (mg/tablet)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine HCl	80	80	80	80	80	80	80	80	80
PVP K30	25	25	25	50	50	50	75	75	75
C0-processed excipient	40	52.5	65	40	52.5	65	40	52.5	65
MCC	125	112.5	100	100	87	75	75	62.5	50
Magnesium Stearate	15	15	15	15	15	15	15	15	15
Talc	15	15	15	15	15	15	15	15	15
Total Weight	300	300	300	300	300	300	300	300	300

The zero-order kinetic describes the system in which the drug release rate is independent of its concentration. The first order kinetic describes the system in which the drug release rate is concentration dependent. Higuchi describe the release of drug from an insoluble matrix as square root of time dependent process. The Hixon-Crowell cube root law describes the drug release from the system in which there is change in the surface area and the diameter of particles present in dosage form. Korsmeyer-Peppas Equation (Diffusion/Relaxation Model) $Mt/M_0 = k5t^n$[18,19]

- Zero order Kinetics $Q = K_0t$
- First order Kinetics $Log\ C = Log\ C_0\text{-}Kt/2$
- Higuchi's Square root of time Equation (Diffusion model) $Q = Kt^{½}$
- Hixon-Crowell cube root Equation (Erosion model) $(100\text{-}W)^{1/3} = 100^{1/3} – k^3t$

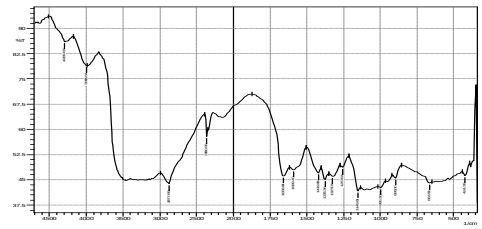
Stability study

Stability studies were carried out as per ICH Q_1A guidelines. The optimized Venlafaxine HCl tablets of F9 batch were wrapped in aluminium foils and were placed in the environmental stability chamber at 40^{0}C±2^{0}C/75%±5% RH for a period of three month. Sampling was done at a predetermined time intervals of initial, 1 month, 2 month, and 3 month. The formulation was analyzed for organoleptic characteristics, hardness, drug content, disintegration time and dissolution profile [20].

RESULTS AND DISCUSSION

Characterization of Co-processed excipient

FTIR spectroscopy is a quick and simple technique for identifying any chemical changes or interaction. FTIR spectra of Chitosan showed characteristic peak at 1157.0 cm-1 due to C-O stretchingand N-H stretching at 1658.44 cm-1. A bending vibration at 1419.66 cm-1 was observed due to CH_3 bending. FTIR spectra of eudragit s-100 exhibits –OH vibrational stretching at 2592.41 cm-1, due to carboxylic acid group, the C=O stretching ester group was found at 1720.56 cm-1. The band present at 1450.52 cm-1, indicating CH_3 bending. As shown in Figure 1. FTIR spectra of co-processed excipients showed retention of all the major peaks of individual polymer which indicate absence of chemical interaction between polymers during processing as Shown in Figure 1.



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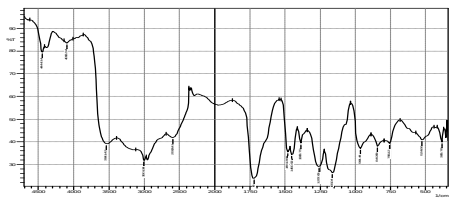

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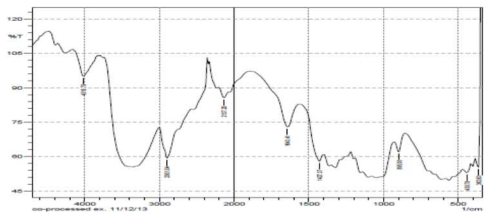
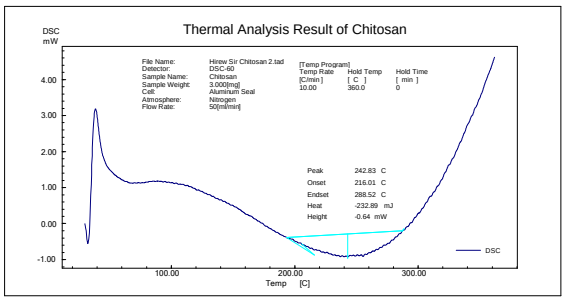


C

Fig. 1: FTIR Spectra of Chitosan (A), Eudragit s-100 (b) and Co-processed excipient (C)

DSC is a useful tool for characterizing a particular polymer based on its exothermic and endothermic thermal transitions. DSC thermo grams of chitosan, eudragit s-100 and (chitosan-eudragit s-100) Co-processed excipients are shown in Figure 2. The DSC thermogram of co-processed excipient exhibits sharp endothermic peak at 244.31 which was corresponding to its melting with decomposition and indicating its crystalline nature and purity of sample. DSC thermogram of co-processed excipients shows no additional endotherm peaks which suggest that developed co-processed excipients are devoid of any chemical changes was shown in Figure 2.



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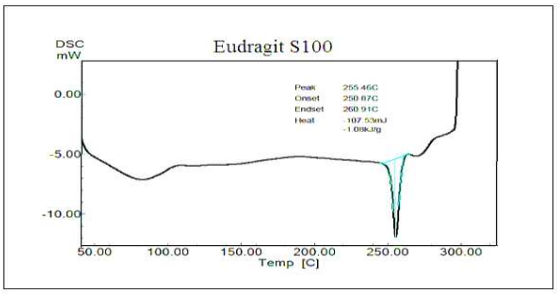

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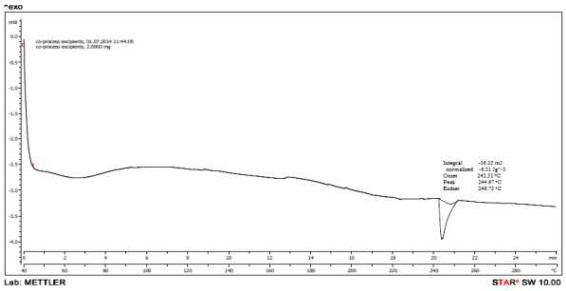
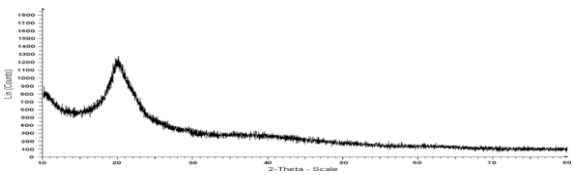


C

Fig. 2: DSC thermogram of Chitosan (A), Eudragit s-100 (b) and Co-processed excipient (C)

The x-ray diffraction patterns of Chitosan, Eudragit s-100, Co-processed Chitosan: Eudragit s-100 has shown in Figure 3. The amount of Co-processed Chitosan: Eudragit s-100 was found 98.90 % amorphous, Chitosan 85.7% amorphous And Eudragit s-100, 88.36% amorphous. And angles and d values stated in [Table 2].



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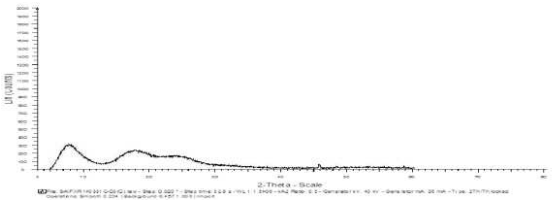

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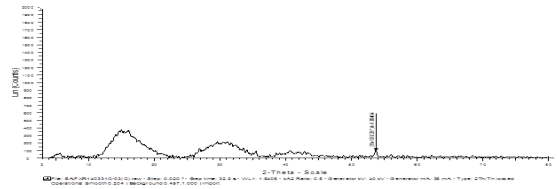
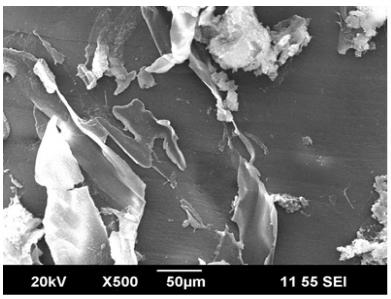


C

Fig. 3: X-ray diffraction pattern of Chitosan (A), Eudragit s-100, and Co-processed excipient (C)

Were also in one range, so no structural changes were found. The x-ray diffraction pattern has shown the diffused pattern indicating the amorphous nature. It has also shown the diffused pattern indicating the co-processed Chitosan with Eudragit S-100 was present in the amorphous state. Hence, it was concluded that the polymorphic characteristic of Chitosan, Eudragit s-100 and their interaction was not changed.

Scanning electron microscopy (SEM) was used to investigate particle surface morphology when comparing the surface of chitosan and eudragit s-100 (1:5) mixture with the surface of co-processed excipient (chitosan: eudragit s-100, 1:5) prepared using solvent evaporation method. It is apparent that its native structure has changed from a smooth, flat surface structure, with folded edges, to three-dimensional compacts for the eudragit s-100. This folding in the surface of the co-processed chitosan-eudragit s-100 creates a bigger surface area which can accommodate a larger quantity of eudragit s-100. As shown in Figure 4.



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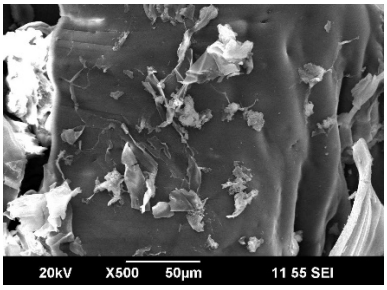


B

Fig. 4: Scanning electron micrograph of mixture of Chitosan + Eudragit s-100 (1:5) ratio (A) and of prepared co-processed excipient by solvent evaporation method (B)

Physical properties of material to be used as an excipient in direct compression formulations are of critical importance. Therefore, physical processes such as mixing, bulk particle movement and compaction are mainly depending on the powder particle characteristics.

The efficiency of flowability of a direct compressible excipient in automated technology employing rotary compression system is essential for production of tablets with uniform weight. The flow and compressibility characteristics of co-processed excipient were indirectly assessed by determining their bulk density, tapped density, angle of repose and Carr's compressibility indices and hausner's ratio.

Results depicted in [Table 3], suggested that all the co-processed excipients have improved flow ability and compressibility. Co-processed excipient prepared in Chitosan and Eudragit s-100 ratio of 1:1, 1:3 and 1:5.

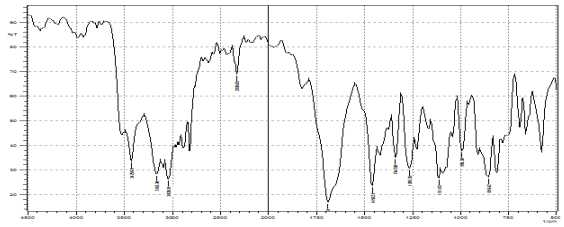
But result of ratio 1:5 showed good flow properties and compressibility as compared to other ratios of selected combinations. The optimized ratio 1:5 also showed good tableting properties as shown in [Table 3]. The compatibility study was carried out to find out compatibility between drug and excipients used in the formulations. The FT-IR spectrum of the pure drug Venlafaxine HCl, Venlafaxine HCl with PVP K30, Venlafaxine HCl with Co-processed excipient, and combination of Venlafaxine HCl matrix tablet formulation are compared with standard spectrum and characteristic band observed as shown in Figure 5. The characteristic bands of Venlafaxine HCl were found at 1388.65 cm^{-1} (C-H Bending) 1493.3 cm^{-1} alcohol (C-0 Stretching) 1610.8 cm^{-1} amine (N-H Bending), 2933.53 cm^{-1}(C-H Stretching) 3326.98 cm^{-1}(0-H Stretching) due to presence of hydroxy, amine and functional group and aromatic ring in the structure of Venlafaxine HCl was shown in Figure 5.

Table 2: Angle and d values in XRD

S. No.	chitosan: eudragit S-100 (Co-Processed excipient)		Native Chitosan		Native Eudragit S-100	
	Angle	d value	Angle	d value	Angle	d value
1	12.984	7.022	9.651	8.651	12.205	6.609
2	13.211	6.697	6.351	7.637	16.551	5.356
3	15.306	5.782	15.386	6.695	17.857	4.964
4	18.023	4.911	18.301	20.236	18.882	4.694
5	19.036	4.626	20.651	21.653	21.732	3.742
6	22.324	3.971	33.213	26.382	23.715	2.781

Table 3: Powder flow properties of co-processed excipient

S. No	Formulation co-processed excipient	Bulk density (gm/ml)	Tapped density (gm/ml)	% Compressibility	Hausner's ratio	Angle of repose(θ°)
1	Chitosan+Eudragit S-100 ratio 1:1	1.111	1.25	11.12 %	1.125	22.82
2	Chitosan+Eudragit S-100 ratio1:3	0.1144	0.1960	11.02 %	1.123	25.46
3	Chitosan+Eudragit S-100 ratio1:5	0.222	0.2666	12.61%	1.200	20.32



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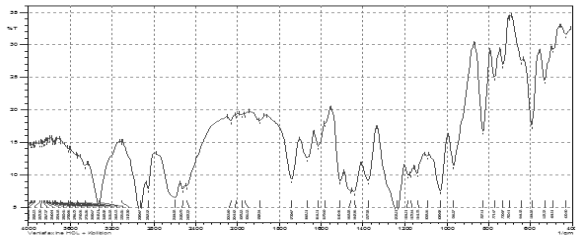

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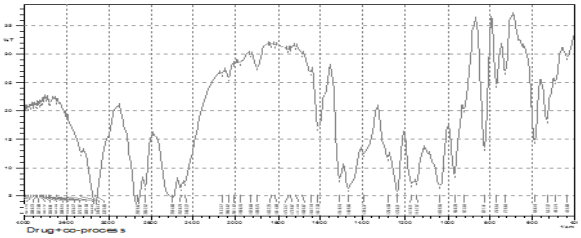

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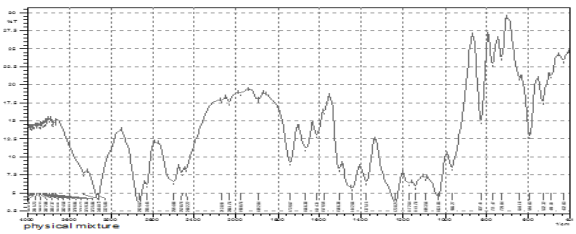

D

Fig. 5: FTIR spectrum of Venlafaxine HCl (A), Venlafaxine HCl+PVP K30 (B), Venlafaxine HCl +Co-processed excipient (C) and physical mixture

The characteristic peak of Venlafaxine HCl with PVP K30were found at 1377.08 cm^{-1} (C-H Bending) 1039.92 cm^{-1} alcohol (C-O Stretching) 1614.31 cm^{-1} amine (N-H Bending), 2929.67 cm^{-1}(C-H Stretching) 3325.05 cm^{-1}(OH Stretching). The spectrum of Venlafaxine HCl with Co-processed excipient shows that at 1396.37 cm^{-1} (C-H Bending) 1039.36 cm^{-1} alcohol (C-O Stretching) 1612.37 cm^{-1} amine (N-H Bending), 2929.67 cm^{-1}(C-H Stretching) 3325.05 cm^{-1}(OH Stretching). The physical mixture shows that all the principle peak of Venlafaxine HCl in physical mixture were preserved and shows at 1375.15 cm^{-1} (C-H Bending) 1031.85 cm^{-1} alcohol (C-O Stretching) 1614.31 cm^{-1} amine (N-H Bending), 2929.67 cm^{-1}(C-H Stretching) 3325.07 cm^{-1}(OH Stretching). Hence, we can conclude that there was no interaction of drug and excipients.

Thermal analysis of drug and its mixture were carried out using DSC. The DSC thermogram of Venlafaxine HCl and its mixture showed sharp endothermic peak at 207.42 °C corresponding to its melting with decomposition and indicating its crystalline nature. The DSC

thermogram of plain Venlafaxine HCl and its mixture is given in Figure 6 and Figure 7. The study showed and confirmed that there is no interaction of Venlafaxine HCl with other selected excipients.

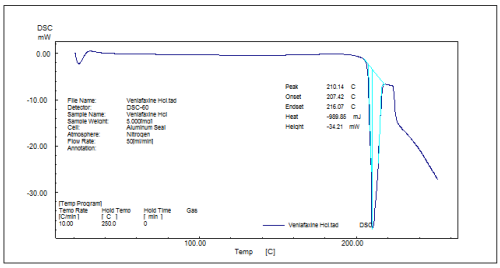

Fig. 6: DSC thermogram of Venlafaxine HCl

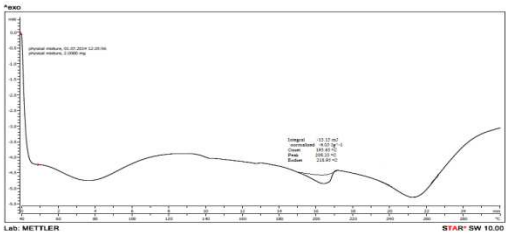

Fig. 7: DSC thermogram of drug and physical mixture of excipient

The powder flow characteristics of drug affect formulation of tablets. The result was shown in [Table4] indicated that the powder blend has good flow property.

Table 4: Blend flow properties of of Venlafaxine HCl tablet formulation

S. No.	Formulation	Angle of Repose	Bulk density	Tapped Density	Carr's Index	Hausner's Ratio
1	F1	22.08±0.30	0.3605	0.4410	18.25	1.22
2	F2	19.95±0.28	0.3947	0.4466	16.70	1.05
3	F3	19.52±0.31	0.3948	0.4414	10.65	1.11
4	F4	21.06±0.42	0.3947	0.4681	15.66	1.18
5	F5	22.10±0.52	0.3750	0.4166	9.98	1.11
6	F6	20.96±0.16	0.4166	0.4682	10.98	1.12
7	F7	18.79±0.28	0.3940	0.4413	10.65	1.12
8	F8	19.40±0.33	0.3801	0.4217	9.73	1.10
9	F9	18.60±0.58	0.3637	0.4231	4.47	1.04

All formulations batches F1 to F9 were evaluated for physical properties such as tablet hardness, weight variations, thickness, diameter and drug content by reported method and found to be in Pharmacopoeial acceptable range. The matrix tablet formulations were prepared using directly compressible coprocessed excipient with composition of 1:5 ratio of chitosan and eudragit s-100 From [Table 5], it was observed that thickness of the tablets for all the formulations was found to between 3.33 mm to 3.46 mm, the maximum standard deviation in thickness was up to 0.028 mm. The hardness of the tablets was found to be in the range 6.7 kg/cm^2. The friability of the tablets for all the formulations was found to be between 0.716 % and 1.00 %.

The average weight of the tablets from all the formulation was found to between 298.33 mg to 302.40 mg.% drug content for all formulation was found to between 98.0 % and 100.02 %.

Table 5: Evaluation of Venlafaxine HCl matrix tablets formulation

Formulation batch	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Average wt. (mg)	Drug content (%)
F1	3.38± 0.028	7.0±0.92	0.716	302.40±0.89	98.0%
F2	3.44± 0.016	7.2±0.37	0.886	298.58± 0.68	97.53%
F3	3.33± 0.024	7.46±015	0.977	300.77± 0.73	99.18%
F4	3.43± 0.024	7.4±0.10	0.73	298.06± 0.69	98.59%
F5	3.38± 0.012	6.7±0.25	0.99	300.83± 0.88	99.82%
F6	3.38± 0.032	7.0±0.50	1.00	299.50± 0.69	98.35%
F7	3.41± 0.0081	6.9±0.26	0.76	299.20± 0.70	99.77%
F8	3.46± 0.0081	7.2±0.025	0.867	298.65± 0.70	99.88%
F9	3.35± 0.024	7.3 ±0.34	0.829	298.69± 0.41	100.0%

Data represented as mean ± Std. Dev. with n=3, Where n= Number of replicates

Table 6: Kinetic treatment of prepared Venlafaxine HCl matrix tablets

Formulation Code	Zero Order (R^2)	First Order (R^2)	Hixson Crowell (R^2)	Higuchi (R^2)	Korsmeyer Peppas	
					(R^2)	(n)
F1	0.9455	0.9328	0.966	0.9894	0.9447	0.4891
F2	0.9651	0.9548	0.9577	0.9993	0.9489	0.6297
F3	0.9577	0.9436	0.9463	0.9781	0.9138	0.5504
F4	0.9762	0.9704	0.9723	0.9883	0.9113	0.4688
F5	0.9522	0.9809	0.9822	0.9904	0.9206	0.4812
F6	0.9513	0.9784	0.9801	0.994	0.9279	0.5028
F7	0.9594	0.9363	0.9354	0.9931	0.9551	0.4753
F8	0.949	0.9513	0.9467	0.9953	0.9458	0.4716
F9	0.9497	0.9529	0.9548	0.9934	0.9226	0.6485

[Table 7] the thickness of optimized F9 formulation was found to be in the range of 3.35- 3.37 mm. Tablet weight was found to be in the range of 298.23-300.77 mg. Hardness of tablets was found to be in the range of 5.20-5.36 kg/cm^2. Content uniformity was found to be in the range of 98.86-99.56 %.

Table 7: Evaluation of formulation (F9) kept for stability at 40^{0}C /75%RH

Parameter	1 Month	2 Month	3 Month
Appearance	White Color	White Color	White Color
Thickness (mm)	3.37	3.37	3.35
Hardness (Kg/cm^2)	5.36	5.36	5.20
Weight of tablet	300.77	299.60	298.23
λ max (nm)	225.00	225.00	225.30
Drug content (%)	99.40	99.56	98.86

The stability dissolution profile optimized F9 formulation are depicted in the Figure 9, Short-term accelerated stability data obtained for optimized formulation revealed that drug content, thickness, hardness, in-vitro dissolution were not significantly changed under accelerated storage condition of 40 ^{0}C ± 2 ^{0}C / 75% ± 5 % RH

The dissolution studies were carried out for all nine formulations i. e. F1 to F9 was shown in Figure 8. Drug content of each tablet was 80 mg and 900 ml of dissolution medium was used for dissolution studies. Maintaining sink condition is important during the dissolution experiment for consistent and accurate measurement of the dissolution rate. Figure.8, it was observed that F9 formulation was found to be optimized formulation and release the drug up to 98.70% for 24 h in a sustained manner as compared to other formulations.

The dissolution data of batches F1 to F9 was fitted to Zero order, First order, Higuchi and Korsmeyer - peppas models [Table 6]. The preference of a certain mechanism was based on the correlation coefficient "r"for the parameters studied, where the highest correlation coefficient is preferred for the selection of the mechanism of release. The highest "r" value was obtained for Higuchi model, so it followed diffusion was the predominant release mechanism for matrix tablets results were in [Table 6]The value of release exponent"n" obtained from Korsmeyer equation was greater than 0.5 for F9- 0.6485 indicate Non -Fickian transport so the final mechanism of drug release was swelling or chain relaxation of polymers followed by diffusion and erosion and the drug releases by first order phenomenon as there was continuous increase in percent cumulative drug release up to 24 hours.

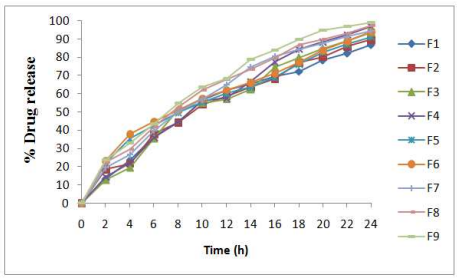

Fig. 8: Cumulative percent drug release profile graph of F1 to F9 Formulation

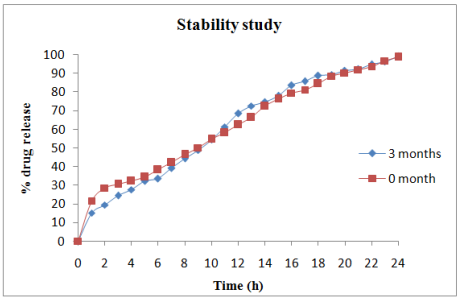

Fig. 9: Stability profile F9 (3 Month)

CONCLUSION

Based on the studies it was concluded thatCo-processed excipients (chitosan: eudragit s-100) were prepared in ratio 1:1, 1:3 and 1:5 by using Solvent evaporation method. The developed co-processed excipients were evaluated for Compressibility index (Carr's index), Hausner's ratio and Flow properties (Angle of Repose). The prepared co-processed excipient in the ratio of 1:5 showed excellent flow properties as compared to other ratio and native excipient like chitosan and eudragit s-100. Hence co- processed excipient in ratio 1:5 was select and use in sustained release matrix tablet of Venlafaxine Hydrochloride and evaluated for Pre-compression parameter such as bulk density, tapped density, Carr's index, Hausner's ratio, Angle of repose, and Post- compression parameter such as hardness, thickness, friability, weight variation, *In-vitro* drug release. Developed co-processed excipient showed good drug release retarding property and could be alternate way to overcome the problems associated with single polymer alone.

All the prepared formulation shows satisfactory organoleptic properties. Drug content of all the developed formulations was found within limits i. e. 98-101%. Once daily matrix tablets of Venlafaxine HCl were prepared using Co-processed excipient and, PVP K-30. The presence of PVP K30 reduces initial swelling of co-processed excipient and retards the drug release up to 24 hours. The presence of Co-processed excipient sustains the drug release due to formation of gel layer around the tablet and PVP K30 releases drug slowly over prolong period of time by forming pores. This investigation clearly indicates that the combination of PVP K30 and Co-processed excipient could be used as retardant of drug release for a period of 24 hours. Various tablet evaluation parameters like thickness, hardness, friability, weight variation and drug content of all formulations were found to be satisfactory. Dissolution study revealed that formulations F9 release the drug up to 24 hours. All formulations showed Higuchi drug release kinetics. All formulation followed zero order kinetics. All formulations were fitted in Korsmeyer Peppas equation. The releases exponent ranges between 0.40-0.70. The optimized formulation (F9), in short-term accelerated testing done for three months at 40^{0}C, there has been no significant difference in dissolution profile, drug content, hardness and physical appearance so formulation should be stable. Venlafaxine HCl matrices could be developed with desirable release modulation for a once daily administration.

CONFLICT OF INTERESTS

Declared None

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REFERENCES

1. Russell R. Synthetic excipient challenge all-natural organics offer advantages challenges to developer and formulators. Pharm Tech 2004;27:38-50.
2. The International Pharmaceutical Excipient Council Excipient Composition Guide. Europe: 2009.

3. Bansal AK, Nachaegari SK. Co-processed excipient for solid dosage form. Pharm Technol 2004;2:52-64.
4. Ogaji IJ, Nep EI, Peter JD. Advances in natural polymers as pharmaceutical excipients. Pharm Anal Acta 2012;3:146.
5. Ayyapan J, Umapathi P. Development and evaluation of a directly compressible Co-processed sustained release agent for tablets. Int J Pharm Sci 2010;2:201-5.
6. Panda B, Raot A, Kilor V. Co-processed excipients: an overview of formulation aspects, physical characteristics& role as a pharmaceutical aid. Pharmatutor-Art1049; 2010.
7. MH Rubinstein. Tablets. In: AULTON ME. (Ed). Pharmaceutics: the science of dosage form design. London: ELBS Longman Group Ltd; 1988. p. 304-21.
8. George M, Abraham ET. Polyionic hydrocolloids for the intestinal delivery of protein drugs: alginate and chitosan—a review. J Control Release 2006;114:1–14.
9. Sanford PA. Chitosan: commercial uses and potential applications; 1989. p. 51-69.
10. Meenakshi joshi. Role of eudragit in targeted drug delivery. Int J Curr Pharm Res 2013;5:57-62.
11. Moustafine RI, Kemenova VA, van den Mooter G. Characteristics of interpolyelectrolyte complexes of Eudragit E 100 with sodium alginate. Int J Pharm 2005;294(1-2):113–20.
12. British Pharmacopoeia Published by The Department of Health, United Nations, Volume II, Venlafaxine Hydrochloride; 2009. p. 6317-20.
13. Raju G. Formulation and evaluation of extended release matrix tablets of venlafaaxine hydrochloride. J Adv Pharm Sci 2012;2(1):240-65.
14. Gohel MC, Jogani PD. A review of co-processed directly compressible excipients. J Pharm Sci 2005;8(1):76-92.
15. Coates J. Interpretation of infrared spectra, a practical approach. John Wiley & Sons Ltd, Chichester, Meyers RA, editors. Encycl Anal Chem 2000. p. 10815–37.
16. Skoog DA, Holler F, Nieman S. Principles of instrumental analysis. Fifth Edition: Thomson Asia Pvt. Limited Singapore; 1996. p. 410-3.
17. Anthony CM, Osselton MD, Widdop B. editors. Clark's Analysis of Drugs and Poisons. Pharmaceutical press Publication: Third Edition; 2005;2: p 598.
18. Higuchi T. Mechanism of sustained action medication. theoretical analysis of rate of release of solid drug dispersed in solid matrices. J Pharm Sci 1963;52:1145-9.
19. Korsmeyer RW, Meerwal E, Peppas NA. Solute and penetrant diffusion in swellable polymers. ii. verification of theoretical models. J Polym Sci Polym Phys Ed 1986;24:409-34.
20. Cartensen JT. Drug stability: principle and practices, edited by Marcel Dakker, 2nd ed. New York; 1999. p. 538-50.