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To Formulation & Evalution Of Oral Fast Dissolving Tablet Of Vortioxetine Hydrobromide.

Name : Shrikant Gopalrao Agarkar , Prof. Miss.Ashwini Wakde,

Dr.Megha T Salve .

College Name : Shivajirao Pawar College of Pharmacy ,

Pachegaon ,Tal .Newasa ,Dist .Ahmednagar.

Corresponding Author : Shrikant Gopalrao Agarkar

ABSTRACT: The end of the present study was to formulate and estimate the fast dissolving tablets of Zidovudine. Zidovudine is an antiretroviral medicine generally used in the treatment HIV infection. The superdisintegrants used in this study was sodium bounce glycolate and cross Carmellose sodium by sublimation system. The tablets were estimated for weight variation, hardness, wetting down time, frangibility, water immersion rate and decomposition time and In vitro dissolution study. The tablets were prepared by direct contraction system. All tablet phrasings showed quick decomposition time, which is veritably characteristic of fast dissolving tablets. All the phrasings showed rapid-fire chance medicine release(28.42- 98.51)). The rapid-fire medicine decomposition(18 sec) was noticed in F8 expression when compare to other expression, which release 98.51 at the end of 30 twinkles. The fast dissolution might be due to quick decomposition of the tablet to form patches and rapid-fire immersion will reuse superdisintegrant was considered as the optimised expression. The in vitro medicine release profile of the optimised expression is F7.

KEYWORDS: Direct compression, Fast dissolving tablet, Cross Carmellose Sodium, Sodium Starch Glycolate, Sublimation technique, Zidovudine.

- **Introduction**
- **Orodispersible films**

The fast- dissolving flicks used for oral medicine delivery are produced using hydrophilic polymers or a combination of polymers to insure they disperse and dissolve effectively in the mouth. By being fleetly absorbed through the vascular mucosa, these flicks avoid first- pass metabolism and can therefore enhance drug bioavailability.

Oral flicks, which are occasionally called oral wafers, are thin layers that are taken by mouth. The third kind oral film delivery styles have been around for a while but have only lately gained attention in the debate over quick medicine immersion. Dissolvable over-the-counter(OTF) or overthe-counter(zilches) breath strips have developed from sweetmeat and dental care breath strips into a unique and well- known delivery system for vitamins and particular care goods. Organizations that have previous experience producing polymer coatings for transdermal medicine administration have expanded this fashion to OTF forms. For the systemic administration of untoward APIs, the use of OTFs has been shown effective, and it's presently prompt to medium phases of development for tradition medicines. Categorization of fast-dissolving technology

Fast dissolve technologies can be characterized into three major categories for simplicity of description.

- **Lyophilized systems.**

On a global base, this system has the biggest deals value, the loftiest volume, and the most product blessings. Tablet- shaped realities can be manufactured with these ways by exercising earth or fester packaging to transfigure a pharmacological suspense or result into the asked shape. After that, the tablets or units are lyophilized and placed in the freezer. The pervious structure enables accelerated water or slaver saturation and biodegradation. These systems' capability to regulate boluses depends on whether the active constituents are answerable or undoable. Tablet- grounded systems have a mainly advanced cure operation capability than answerable drugs, which have a significantly lower capacity. Units, as opposed to tablets, can have flavor- masking constituents and dissolve more snappily.

- **Compressed tablet-based systems.**

Excipients are compressed to form this system. Tablet technologies are moreover robust or delicate, depending on the product process. This leads to different packaging conditions for decomposition effectiveness, ranging from HDPE holders or pocks to more customized designs for quality control, similar as those offered by CIMA Labs, PackSolv, and others. Tablets that dissolve snappily and contain bouncy, super disintegrated or water-answerable constituents allow water to be fleetly absorbed. These capsules are appertained to as" bouncy factors". BiovailFuisz Technology is an exception among tablets. Shearform develops sugar fluff for tableting invested with colorful medicines and excipients. These systems can handle high boluses of drugs, including patches with concealed flavors. Thin film and lyophilized lozenge forms deteriorate more snappily. Some technology enterprises, ingrained pots, and pharmaceutical companies manufacture line extensions and general fast- dissolving cure forms in- house using loose contraction tablets.

➢ **Types of OFDF based on dissolving technologies**

There are three types of OFDF based on the way they disintegrate in the mouth

➢ **Flash release**

- They are usually single-layer films, highly soluble and made with hydrophilic polymers
- They are usually placed on the tongue
- The dissolution time for these variants is 60 seconds or less and the site of action is both systemic and local

➢ **Mucoadhesive melt-away wafer**

- They can be either single-layer or multilayer and are formed from highly soluble hydrophilic polymers
- Typically, the drug phase in these systems is created as either suspended drug particles or a solid solution, and they are applied to either the buccal or gingival area.
- Within a few minutes, it disintegrates, forming a gel
- It can work in both systemic and local

➢ **Mucoadhesive sustained-release wafers**

- It is also a multilayer system formed from excipients that are non-soluble polymers.
- The drug phase is usually a solid or suspended solution
- The application site is generally in the gingival region
- It takes a longer duration for dissolution, usually 8 to 10 hours

➢ **Advantages and Limitations of oral films**

➢ Oral disintegrating Flicks(ODFs) have several advantages over regular specifics, including fast dissolution time and ease of operation. The unique parcels, similar as high mechanical strengths and low- cost lyophilization processes, have made ODFs a largely precious product in the pharmaceutical assiduity(Arya, Sharma et al. 2010). In discrepancy, the precious packaging system and restriction in high- cure lading are the limitations of oral flicks. Since flicks dissolve in the mouth, they must be palatable and scrumptious. medicines with unwelcome tastes and odors must be tastemasked, which tends to limit the quantum of medicines in the film. It's preferable to reuse under controlled circumstances with low relative moisture because indeed a small quantum of humidity immersion in flicks could beget sticky flicks and stability problems. Enzyme impediments are used in flicks to help proteolytic enzyme function because protein- and peptide- grounded specifics can only be integrated if their exertion is disencumbered.

➢ Materials & Equipments

- **Materials**

S No	Materials
1	**Vortioxetine hydrobromide**
2	**HPMC E-15**
3	**PVA**
4	**Mannitol**
5	**PEG 600**
6	**Glycerol**
7	**Aspartame**
8	**Maltodextrin**

Table: List of materials used

- **Equipments**

S.No	Instruments	Manufacturer
1	Weigh balance (Electronic)	Shimadzu
2	FTIR- infrared spectrophotometer	Shimadzu
3	DSC	Shimadzu DSC-60 Plus Thermal Analyzer, Japan
4	Tablet punching machine (12 station)	Delite Tablet Punching Machine,Vadodara
5	Friability test apparatus – Roche friabilator	Meta Lab Scientific Industries, Mumbai India
6	Disintegration test apparatus	DBK Instruments, Mumbai
7	Monsanto hardness tester	Pathak Electrical Works, Mumbai
8	Dissolution tester (TDT-14L USP)	Electrolab, Banglore, India

Table: List of instruments used

➢ Preparation of Oral Fast dissolving films

Vortioxetine Hydrobromide oral disintegrating flicks were produced using the solvent casting system. To produce the needed results, maltodextrin was dissolved in purified water and stirred to form an waterless result I with a attention of 10 w/ v. also, mannitol was dissolved in purified water while stirring to produce waterless result II, which had a mannitol attention of 10 by weight. Polyvinyl alcohol was dissolved in purified water using a mild heating process at 40 ° C to produce waterless result III, which included polyvinyl alcohol at a attention of 2 w/ v. In agreement with the quantitative formula, HPMC- E15 was dissolved in a solvent admixture made up of 15 to 25 ml of each of the waterless results I, II, and III. Under shifting, glycerin, cut 600, and aspartame were added to the admixture. A small quantum of methanol was used to dissolve the drug. Next, while stirring, the medicine result was added to the polymeric result. The performing result was stirred sluggishly for 30 twinkles to exclude any bubbles. Using amicro-meter film applicator, the result was cast onto glass plates to form flicks, which were dried overnight or subordinated to a temperature of 40 °C for 12- 14 hours, or 50 °C for 78 hours. The dry flicks were precisely removed from the glass

plates and audited for any blights. latterly, they were cut into the needed confines. The samples were maintained in a glass vessel until farther examination at a temperature of 25 °C ± 2 °C and a relative moisture of 75 °C ± 5.

Table: VortioxetinevHydrobromide Oral Fast Dissolving tablet

Formulation (mg/film)	F1	F2	F3	F4	F5	F6	F7
Vortioxetine hydrobromide(mg)	10	10	10	10	10	10	10
HPMC E-15	15	10	10	5	10	15	10
PVA (2%w/v)	4	4	4	4	4	4	4
Mannitol (10%w/v)	5	5	5	5	5	5	5
PEG 600	4	4	4	2	4	6	6
Glycerol	3	3	3	3	3	3	3
Aspartame	4	4	4	4	4	4	4
Maltodextrin (10%w/v)	5	5	5	5	5	5	5
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

- **Experimental Work.**
- **Preformulation studies of drugs**

- **FTIR compatibility study**

The FTIR study was performed on both the drug and the polymers used in the oral film preparation. The spectral measurements were carried out using a Thermo-IR 200 spectrophotometer manufactured by SAIP (Shimadzu Analytical India Pvt. Ltd). To disperse the oral films, KBr (potassium bromide) pellets were utilized. To evaluate the drug compatibility and any alterations in the drug's form, spectra were achieved on the FTIR spectrophotometer using powder diffuse reflectance. The wavelength range for each spectrum acquisition was set from 400 to 4000 cm^{-1}.

- **Scanning electron microscopy (SEM) of oral films**

For the examination of the surface texture of the developed oral films, SEM (Scanning Electron Microscopy) was employed. The specific SEM instrument used was the Jeol JSM-6100, manufactured in Japan. The analysis was carried out by positioning the oral films sample inside the sample holder. The SEM operates by utilizing a tungsten filament as the electron source. Photomicrographs of the oral films were taken at a magnification of 1000 to capture detailed images of the surface texture. Similarly, refers to the shapes and arrangements of the structures that make up the oral films that were prepared and investigated using SEM.

- **DSC (Differential Scanning Calorimetry)**

The DSC (Differential Scanning Calorimetry) analysis of the oral films was conducted using a DSC instrument manufactured by NETZSCH Technologies India Pvt. Ltd. For the analysis, a DSC pan with a tightly sealed lid was utilized, and an 8mg sample of the oral film was placed inside the pan. The heating process was carried out continuously, with the sample being heated at an estimated 10°C per minute. To create the appropriate experimental conditions, the DSC instrument operated in a liquid nitrogen environment within a temperature range of 20 to 250°C. This controlled environment ensured accurate measurements and allowed for the detection of endothermic events and changes in the thermal properties of the oral films. The DSC technique enabled the measurement of heat flow associated with thermal transitions and phase changes in the sample, providing valuable insights into the thermal behavior and characteristics of the oral films.

➢ **Physical Evaluation**

- **Weight Variation**

The film samples were obtained by cutting them from various positions, including the center and the four corners of each film. The mean weight was determined of each film, and the deviation of each film's weight from the mean was calculated.

- **Thickness**

The diameter of the oral fast-disintegrating films was measured using a screw meter gauge manufactured by Swastik Scientific Instruments Private Limited, located in Maharashtra. Measurements were taken at multiple spots on the film. Corresponding to this, the film's thickness was determined by measuring it in three distinct places and averaging the results. The standard deviation (SD) was also determined to assess the variability in thickness across the film.

- **Folding Endurance**

To evaluate the folding strength of the oral film, a repeated folding test was conducted at the same location on the film. The folding process was continued until the film eventually broke. The number of folds the film could withstand before breaking was used to calculate its folding strength. This quantification provided a measure of the film's ability to withstand repeated folding before reaching its breaking point.

- **Percent Drug Content**

The films were enclosed in 10 ml volumetric flasks with pH 6.8 phosphate buffer to make them ready for analysis. Following a 30 minute sonication session at 25°C, the flasks went through a 15 minute centrifugation process at 5200 rpm. The resulting solutions were filtered through 0.45mm filters before spectrophotometric analysis was carried out.

- **Percent Moisture Content**

The oral films were weighed before being put into a desiccator at room temperature with fused anhydrous calcium chloride. The films were weighed again to ascertain the moisture content % after 24 hours. The formula used to calculate the moisture content was [(Initial Weight - Final Weight)/Final Weight] x 100.

The initial weight referred to the weight of the film before it was placed in the desiccator, while the final weight referred to the weight of the film after 24 hours of storage in the desiccator.

- **Surface pH**

To investigate any potential negative effects *in vivo*, the surface pH of the fast-disintegrating oral films was measured. It was thought necessary to keep the surface pH as close to saliva's pH level as feasible in order to lessen the potential of irritating the oral mucosa. The pH was resolute by placing an electrode on the upper side of the oral film, and this process was repeated three times to obtain an average value. The standard deviation was also calculated and recorded.

➢ **Chemical Evaluation**

- **Disintegration**

To visually determine the disintegration time of the oral films in an *in-vitro* environment, a petri dish containing 10 ml of pH 6.8 phosphate buffer was utilized. The oral film was placed in the buffer and the dish was swirled. The time it took for the film to disintegrate was observed.

- **Dissolution Studies**

To investigate dissolution rates, USP Type-I dissolution equipment, specifically basket-type. Electro Lab dissolving equipment, was used. The experiment was performed in 500 ml of pH 6.8 phosphate buffer, which was kept at 37°C ±5°C with a 50 rpm rotation speed. A 2.5 ml sample was taken each time and replaced with the same volume of fresh pH 6.8 phosphate buffer. The rate at which the samples were dissolving was calculated using spectrophotometric measurement at 238 nm. Same procedure repeated with another drug and the wavelength was selected as 228nm.

- ***In -vivo* permeation studies**

Franz diffusion cells with a 25 ml capacity and a 1.9 cm internal diameter were used by the researchers in their *ex vivo* permeation studies. Porcine buccal mucosa was removed from the ventral tongue surface, washed, and distributed equally across the donor and receptor compartments of the cell. The receptor compartment was filled with 25 ml of 6.8 pH isotonic phosphate buffer at 37 °C and stirred with a magnetic stirrer to preserve hydrodynamics. A single film unit that was 2 cm by 2 cm in size was moistened with a few drops of the same buffer and placed in the donor compartment along with 1 ml of pH 6.8 phosphate buffer. The receptor compartment was regularly emptied of 2 ml of sample and replenished with 2 ml of phosphate buffer at a pH of 6.8. Employing a UV-Visible spectrophotometer and analyzing the absorbance at a maximum wavelength of 238 nm, 228nm they assessed the cumulative percentage of VortioxetineHydrobromide that entered through the buccal mucosa.

- **Stability studies**

EST/VOR containing oral fast-dissolving film formulations were tested for stability by exposing optimized batches for three months to accelerated conditions of 40°C and 75° %RH. For further investigation of significant quality factors, each film was first wrapped with butter paper, followed by aluminum foil and plastic tape, and then kept in glass containers. The EST/VOR oral rapid dissolving films were examined for their drug concentration, surface pH, and drug release effectiveness after three months

➢ Results and Discussion.

- **FTIR Compatibility Studies**

In the study, the compatibility of Vortioxetine (a drug) with different polymers (HPMC, maltodextrin, and PVA) was investigated by comparing and evaluating their FTIR spectra. A range of wavenumbers were used to observe the FTIR peaks. The functional groups they represented included N-H stretching, C=C aromatic stretching, C-H aromatic stretching, CH_3 stretching, CN stretching, and C-S-C stretching. Based on the analysis of the I.R. spectra of the pure drug and drug-polymer blends, it was determined that there was no incompatibility between the drug and polymers. The N-H stretching band, the C-H aromatic stretching band, and the C=C aromatic stretching band were all seen at 3310-3416 cm-1, 3060-3096 cm-1, and 1450-1485 cm–1 respectively. The CH_3 stretching band at 1340-1370 cm-1 and the CN stretching band at 13151401 cm-1 both showed similar compositions. Therefore, it can be said that Vortioxetine oral films can be created using any of the polymers that were investigated.

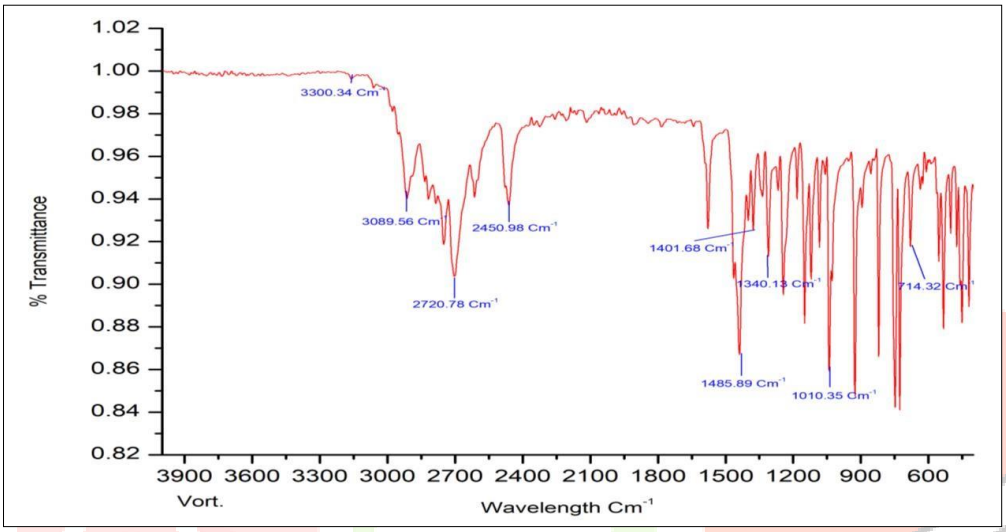

Figure: FTIR graph of VortioxetineHydrobromide

- **SEM**

According to scanning electron microscopy, the medication is disseminated within a very porous polymeric matrix. The results showed that the Vortioxetinehydrobromide was evenly dispersed throughout the polymeric matrix.

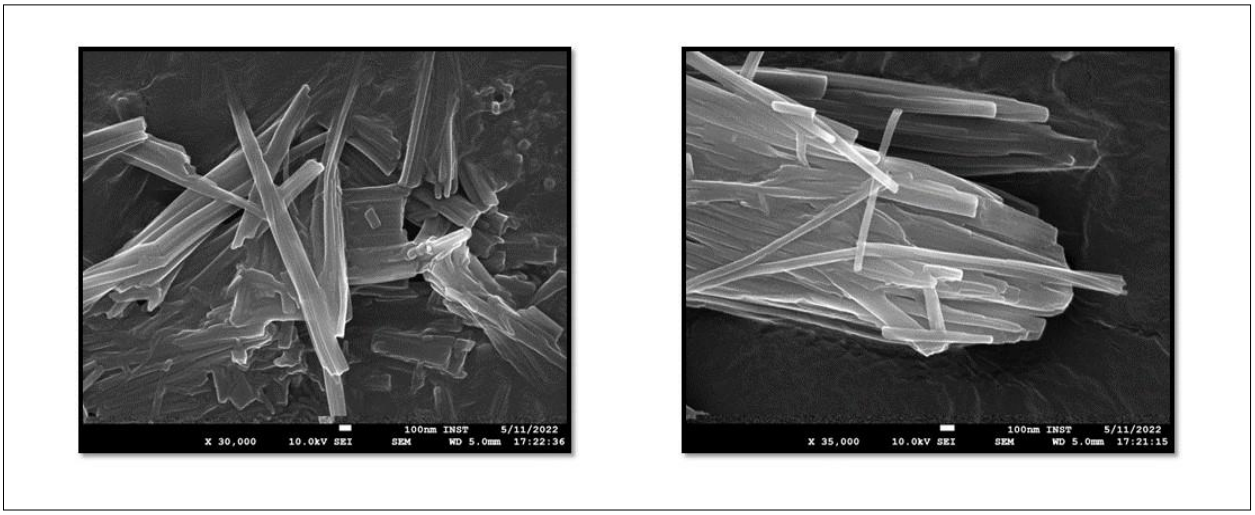

Figure: SEM of (VOR) Oral Fast Dissolving Films

- **DSC**

DSC curves of Drug and polymers were here in performed, and the results are displayed in Figures. It exhibits a melting peak at 230°C and shows similar peaks in polymer DSC graphs.

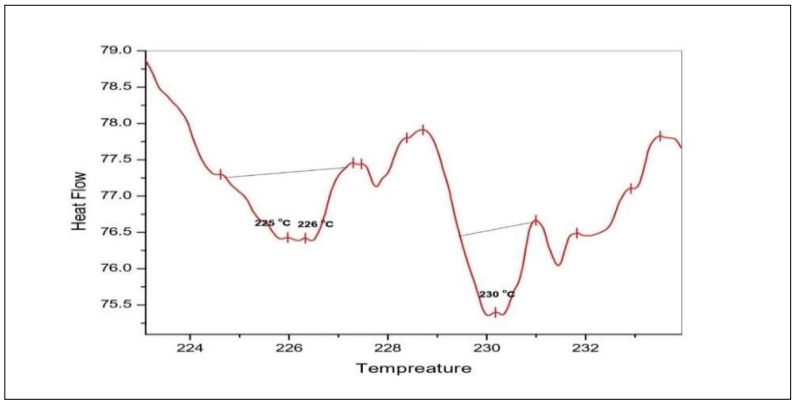

Figure: DSC Thermogram of mixture

- **Physical evaluation**

➢ **Film thickness**

The formulations had thicknesses in the series of 0.10±0.00 mm to 0.22±0.01 mm. The results have been tabulated in Table.

➢ **Weight variations**

The peeling film was divided into three film units at each of the four corners and the center, and the average weight was computed (32.03±0.64 to 34.03±0.23). The outcomes of deviations from average weight are presented in Table.

➢ **Surface pH**

According to Table, the surface pH of the oral fast-dissolving films containing Vortioxetinehydrobromide ranges from 5.03±0.11 to 6.41±0.1. Because salivary pH and the observed surface pH of the formulation were identical, no mouth discomfort was anticipated.

➢ **Moisture Content**

The results of the moisture content varied from 1.33±0.63 to 2.72±0.28 %.

- **Chemical Evalution**

➢ ***In vitro* disintegration**

For VOR film compositions, the in vitro disintegration time ranges from 21 to 31 seconds.

- **Determination of drug content of the films**

The mean and standard deviation of the drug content analyses were computed in triplicate. According to the observations listed in Table, the observed values were within the standard deviation of the mean, indicating that the drug content of oral fast-dissolving film formulations was consistent among films made from various sites according to area and weight. The results were 96.58±0.80 to 99.13±0.96 %.

Table: Evaluation of Oral Fast Dissolving film of VortioxetineHydrobromide

Formulation	F1	F2	F3	F4	F5	F6	F7
Average weight	34.03±0. 23	33.30± 0. 80	33.97± 1.1	33.77± 0.50	33.63±0. 57	33.50± 0. 52	32.03± 0. 64
Folding endurance	300. 0	258. 0	280. 0	150. 0	250. 0	300. 0	280. 0
Surface pH	6.41±0. 53	5.81±1. 0	5.96±0. 02	5.03±0. 11	5.80±0. 22	6.52±0 .01	5.96±1 .10
Thickness (mm)	0.19±0. 0 2	0.17±0. 2	0.18±0. 0 25	0.10±0. 0 0	0.21±0. 0 2	0.22±0 .0 0	0.20±0 .0 0
Drug Content	98.83±0 .12	97.78± 0.30	97.48± 0.35	96.58± 0.80	97.85±0 .23	99.13± 0.96	98.45± 0.46
Moisture content	1.62±0. 9	1.80±1. 2	2.05±1. 4	1.97±0. 6	2.56±1. 10	1.68±1 .37	1.33±0 .63
Disintegration Time	23	27	29	35	28	21	25
Drug Release	7±0.40	91.92± 0.15	92.45± 0.6	84.12± 0.9	91.23±0 .78	99.21± 0.80	96.51± 0.86

- ***In vitro* dissolution study**

The solution of Vortioxetine hydrobromide was scanned to obtain the U.V. spectrum and the absorption maxima in the 200 to 400 nm range. The standard plot of Vortioxetine hydrobromide in Phosphate buffer pH 6.8. By dissolving 100 mg of the drug in methanol and bringing the volume to 100 ml with phosphate buffer pH 6.8, vortioxetine hydrobromide was made into a solution. The buffer solution was then used to create dilutions from this stock solution to create several test solutions with concentrations ranging from 2 to 10 µg/ml. Using a double-beam UV spectrophotometer and a wavelength of 228nm, the absorbance of VOR in various solutions was determined in comparison to a blank phosphate buffer.

VOR in phosphate buffer at 7.4 on a typical plot. A standard solution of Vortioxetine hydrobromide was created by dissolving 100 mg of the drug in 100 ml of methanol and adjusting the solution's pH with phosphate buffer to 7.4. From this stock solution, further dilutions were prepared using the buffer solution to provide several test solutions with concentrations ranging from 2 to 10 µg/ml. The

absorbance of VOR in these solutions was then determined in comparison to a control phosphate buffer using a double-beam UV spectrophotometer (1800 Shimadzu) U.V. Spectrum Analysis.The standard curve for vortioxetinehydrobromide and its UV spectrum analysis scan are shown below.

Table: Standard plot of Vortioxetinehydrobromide in Phosphate buffer pH 6.8

Sr. No.	Concentration(µg/ml)	Absorbance
1	2	0.157
2	4	0.289
3	6	0.417
4	8	0.563

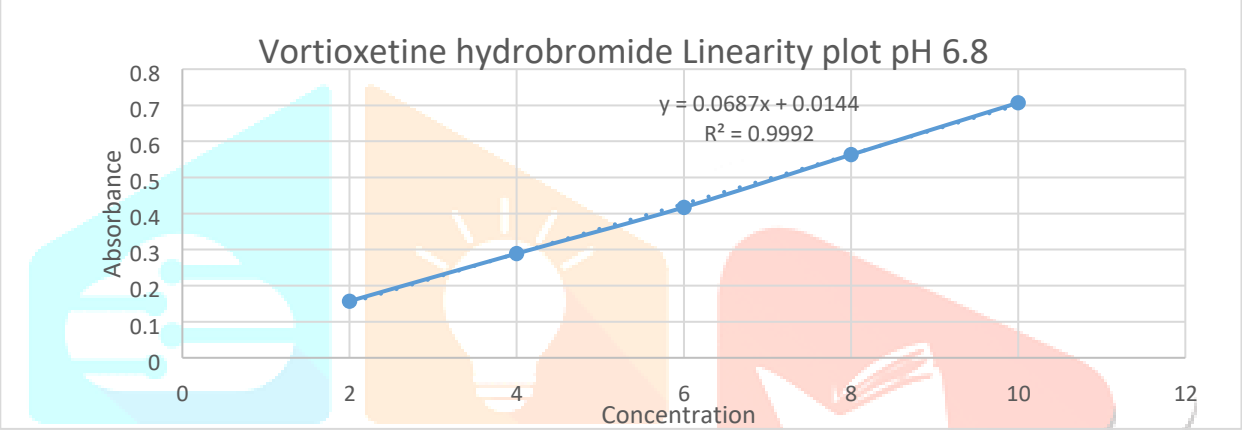

Figure: Linearity plot of Vortioxetinehydrobromide in pH 6.8

Conclusion.

For the oral thin films of escitalopram oxalate and Vortioxetine hydrobromide, suitable filmforming matrices were developed using a combination of polymers such as HPMC E15, maltodextrin, and polyvinyl alcohol. Based on dissolution and permeation studies, a promising formulation called F08 and VOR06 was identified for the rapid release of drugs. The formulation exhibited maximum permeation, desirable flexibility, surface pH, and thickness. The in vitro disintegration time of the films ranged from 24 to 36 seconds for F08 21 to 31 sec. for VOR06. We were demonstrating their fast-dissolving nature. The drug content analysis showed values between 96 % to 99 %, with the formulation (EST) F08 and VOR 06 achieving the highest drug content. HPLC analysis and standard calibration curves confirmed the linearity and accuracy of the drug assay method. F08 and VOR 06 are suitable formulations for the immediate release of drugs from oral films, as shown by their uniformity of content, flexibility, maximum drug release, and significantly enhanced permeation, respectively, with desired surface pH, according to the analysis of results from in vitro drug release and ex vivo permeation studies for Escitalopram oxalate and Vortioxetine hydrobromide oral fast dissolving films. The drug release study in vitro exhibited a rapid dissolution of escitalopram oxalate, with over 90% of the drug dissolved within 6 minutes for most formulations and for Vortioxetine hydrobromide drug release above 90% in 10 minutes. The release rate could be modulated by adjusting the polymer concentration, with higher levels of HPMC E-15 resulting in slower drug release. Stability studies indicate that the films remain stable for up to three months under accelerated stability conditions.

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