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Fabrication, Advancement and Assessment of oral dispersible film of Vardenafil HCl Trihydrate

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ABSTRACT: Oral dispersible films are gaining more attention nowadays due to its lots of advantages including onset of action and better bioavailability. The present work is based on the preparation of oral dispersible film of Vardenafil HCl trihydrate which is used in the treatment of erectile dysfunction. It also have an advantage of avoiding any extra fluid during its administration. Due to presence of blood vessels in oral mucous, the drug get directly circulated in blood stream through the vessels without passing through gastrointestinal tract [GIT] and also away from first pass metabolism. In this formulation, the ingredients which are used are as; Hydroxypropylmethyl cellulose as film former, Propylene glycol as plasticizer, Methyl cellulose as thickening agent, Sucrose as sweetening agent, Disodium EDTA as preservative and Citric acid as saliva stimulating agent. The films were prepared by Solvent casting method and parameters like drug content, content uniformity, tensile strength, folding endurance, in vitro drug release etc. were evaluated.

KEYWORDS: Oral dispersible films, Vardenafil HCl trihydrate, disintegration time.

I. INTRODUCTION

Fast mouth dissolving films (MDFs) or Oral dispersible films (ODFs) can be utilized for administration of a drug systemically to attain medicinal or pharmacological response. ODFs have better systemic bio availability due to avoiding first pass metabolism of drug. ODFs are also suitable for administration as they can be easily placed in oral mucosa or tongue and it disintegrates within few seconds and with the help of blood capillaries present in mouth the drug get easily circulated within blood stream. The ODFs also have advantages for those patients who have swallowing problems and for those who are get treated with anticancer therapies.

The MDFs are when get placed on tongue, they get intimate contact with saliva and disintegration or dissolution takes place which releases the API. The MDFs are usually formulated using hydrophilic polymers due to which instant dissolution takes place with contact with saliva [1].

Specific Characteristics of a Suitable Drug candidate for Mouth dissolving film:

The criteria for selection of the drug candidate for mouth dissolving films include:

- The drug should have a lower dose not more than 30mg.
- The drug must have a good taste.
- The drug should have better solubility in water and saliva.
- The drug should have optimum i.e. lower to moderate molecular weight.
- The drug should be non reactive with the pH of the oral cavity.
- The drug should have better permeability so that it can permeate oral mucosa [2].

Advantages of Mouth dissolving films:

Mouth dissolving films have following advantages:

- Convenient in swallowing for both geriatric and paediatric patients.
- Easy handling.
- Suitable and precise dosing.
- The films do not require water during its administration.
- Easier for patients who are scare of engulfing capsules or tablets.
- Quick action due to avoiding first pass metabolism.
- Better bio availability.
- Decreases choking chances.
- Ease in packaging.
- Reduce adverse effects [2].

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Disadvantages of mouth dissolving films:

Mouth dissolving films have following disadvantages:

- Humidic in nature.
- Only low doses can be incorporated in form of films (< 20 mg).
- Uniforming a dose of exact concentration is practically tough work.
- For the stability and avoiding decomposition of the products, specific packaging is required [2].

II. MATERIALS AND METHODS

MATERIALS: Vardenafil HCl trihydrate was received as a gift sample from Centurion Remedies Pvt. Ltd. Vadodara and other ingredients were purchased from Central Drug House Pvt. Ltd., New Delhi and Thermo Fischer Scientific India Pvt. Ltd., Mumbai.

METHODS

Preformulation Studies:

1. **Identification test of drug (API):** The drug was tested for its identification through FTIR (PerkinElmer Spectrum version 10.4.00) to ensure its identity and purity.
2. **Melting point determination:** The melting point of the API (Vardenafil) was determined by using a melting point apparatus (fig.1).
3. **Solubility profile determination:** For solubility profile determination, 1mg of drug Vardenafil is dissolved individually in 5 ml of solutions of ethanol, methanol, water, Acetonitrile: water. After few minutes the solutions are observed visibly to determine the solubility and recorded whether the drug is dissolved completely or partially or nothing is dissolved in solution.
4. **pH determination:**

The pH of drug was determined by using a digital pH meter in which 5 mg of drug is poured into 10 ml of water in a 50 ml of beaker and mixed completely after that the electrode of the pH meter is poured into the solution and the pH of the film is recorded as resulted by the pH meter.

5. **Drug excipeint compatibility study:** FTIR spectra of pure drug sample, mixture of drug and excipients are tested in Kbr mode for studying about any reaction or compatibility between drug sample and excipients. The physical mixture of drug, film former and other excipients were stored for 30 days with proper packaging at suitable temperature and humidity (40 ± 20 C / 75 ± 5 % RH) and after 30 days the FTIR test of stored sample was recorded.

Figure 1 pH determination by digital pH meter

Figure 2 Film Casting Plate

6. **Spectrophotometric Estimation of Vardenafil HCl trihydrate in Phosphate buffer pH 6.8:**

Standard solution of Vardenafil HCl trihydrate: The solution was formulated by dissolving 10 mg of vardenafil HCl trihydrate in 1000 ml of

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phosphate buffer 6.8 in a volumetric flask (stock solution).

Determination of absorption maxima:

The prepared standard solution of the drug (1µg/ml) was scanned between the ranges of 200-400 nm which showed maximum absorbance at 214 nm. Hence, 214 nm was chosen as the wavelength of highest absorbance i.e. λ max. Calibration curve was plotted by taking absorption of diluted stock solutions (5, 10, 15, 20, 25, µg/ml) at wavelength 214 nm.

Method of formulation (Solvent casting method):

The water soluble polymer (HPMC) was dissolved in water for the formation of a clear thick solution. Another solution was prepared in which API (Vardenafil HCl trihydrate) and other excipients (propylene glycol, citric acid, disodium EDTA, Sucrose) were dissolved with water and mixed in the polymer solution and stirred till the solution get uniform, the solution was then checked for any bubbles if there, it get removed through sonicator and then the solution was casted in the form of thin films into casting plate and kept for drying at 45-50°C in Hot air oven. After the film is get dried completely they get cutter out from casting mould.

Formulation Optimization:

Chemicals /Excipients Used	Quantity Used [for every 12 films]			
	F1	F2	F3	F4
API	240 mg	240 mg	240 mg	240 mg
Hydroxyl Propyl Methyl Cellulose	360 mg	480 mg	600 mg	720 mg
Propylene Glycol	0.03 ml	0.06 ml	0.09 ml	0.12 ml
Methyl Cellulose	12 mg	12 mg	12 mg	12 mg
Sucrose	6 mg	6 mg	6 mg	6 mg
Disodium EDTA	3 mg	3 mg	3 mg	3 mg
Citric acid	24 mg	24 mg	24 mg	24 mg

Table 1 Formulation Optimization

Evaluation Parameters:Tack Test: Tack test refers to the tackiness (stick) of the film which is evaluated by touching the film
with fingers manually and observing whether it is sticky or not.

Thickness Test: The thickness of the film was examined by using a calibrated digital Vernier Calliper which is calculated by selecting 5 random films from each batch, measuring their thickness from five different places (four corners and one centre of film) and calculating their average.

Weight variation test: It is calculated by weighing 5 random films from each batch and calculating their average to determine the weight variation.

Folding Endurance test: It is calculated by folding a film at a same place till it broken down and the number of folding is noted down as its folding endurance.

pH evaluation test:

The surface pH of the film was calculated by placing a randomly selected film from each batch in a petridish and moistening the film by 0.5 ml of water. After few seconds the electrode of the pH meter was bring in contact with the formulation and pH was recorded when stabled.

International Journal of Pharmaceutical Research and Applications
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Figure 3 Prepared Oral dispersible films

Tensile strength test:

It refers to the maximum stress applied to a point at which the film breaks. It was performed by using a TA.XT 2 texture analyser in which film strips were hold in middle of two clamps fixed at a distance of 3 cm. Then the strips were snatched by the upper clamp at a rate of 2 mm/s and the force was determined when the films breaks [46]. It is calculated by:

$$\mathbf{TS} = \frac{\mathbf{Load\ at\ failure} \times \mathbf{100}}{\mathbf{film\ thickness} \times \mathbf{film\ width}}$$

In-vitro disintegration test:

This test was performed by petridish method, 2ml of distilled water was taken in a petridish and the film was poured into it and the time required for dissolving film was noted as its disintegration time. This method was revised for every batch in triplicate form and the average disintegration time was derived for each batch.

Percentage moisture absorption:

It is generally determined to examine the physical stability of the MDFs in humid conditions. In this method, three films were taken, weighed and kept in desiccators containing saturated solution of aluminium chloride. After 24 hours films were withdrawn, weighed and percentage moisture absorption was calculated using the formula mentioned below.

$$\text{PMA} = \frac{\text{Final weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100$$

Percentage moisture loss:

It is usually calculated to determine the integrity of MDFs in dry conditions. Three films were weighed and kept in desiccators containing fused anhydrous calcium chloride. After 24 hrs film were withdrawn and weighed and the percentage moisture loss was calculated using this formula [50]:

$$\mathbf{PML} = \frac{\mathbf{Initial\ weight} - \mathbf{Final\ weight}}{\mathbf{Initial\ Weight}} \times \mathbf{100}$$

Drug content uniformity:

Drug content uniformity was determined by UV spectrometric method in which films from each batches was taken in 100 ml volumetric flask containing methanol, after stirring 10 mins the volume was made up to 100 ml. From this solution 5 ml was taken out in a 50 ml of volumetric flask and volume was made up to 50 ml. After that the solution was filtered and absorbance was taken at 214 nm and drug content uniformity was determined by plotting standard curve of drug.

In-vitro dissolution study:

The dissolution study was determined using USP type II (paddle apparatus) by using 500 ml of 0.1 N HCl having 0.5 % W/V Sodium Lauryl Sulphate, as dissolution medium was maintained at 37 ±0.5ºC. Medium was stirred at 100 rpm for time duration of 1 hour. Samples were taken out at every 15-min interval, refreshing the same amount with the fresh medium. Samples were specifically diluted with methanol and observed for drug content at 285 nm through UV spectrophotometer.

SEM (Scanning electron microscopy) analysis:

The surface morphology of the oral dispersible film has been observed by using scanning electron microscope, (Nova Nano SEM 450). The samples were fitted to the slab surfaces with both sided adhesive tapes and the scanning electron photomicrograph was observed at 1000X magnification. The SEM was performed for a dummy formulation (without API) and for F3 formulation on the basis of accuracy of evaluation data of F3 formulation.

Accelerated Stability Studies:

The stability studies of the formulation F3 & F4 were carried out by storing the films at a temperature of 40± 2°C and RH 75± 5%. The samples were withdrawn for analysing various evaluation parameters at 10, 20, 30, 40, 50 & 60

International Journal of Pharmaceutical Research and Applications
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days respectively to determine the stability of the films.

III. RESULTS AND DISCUSSION

Preformulation studies:

Identification test of drug (API):

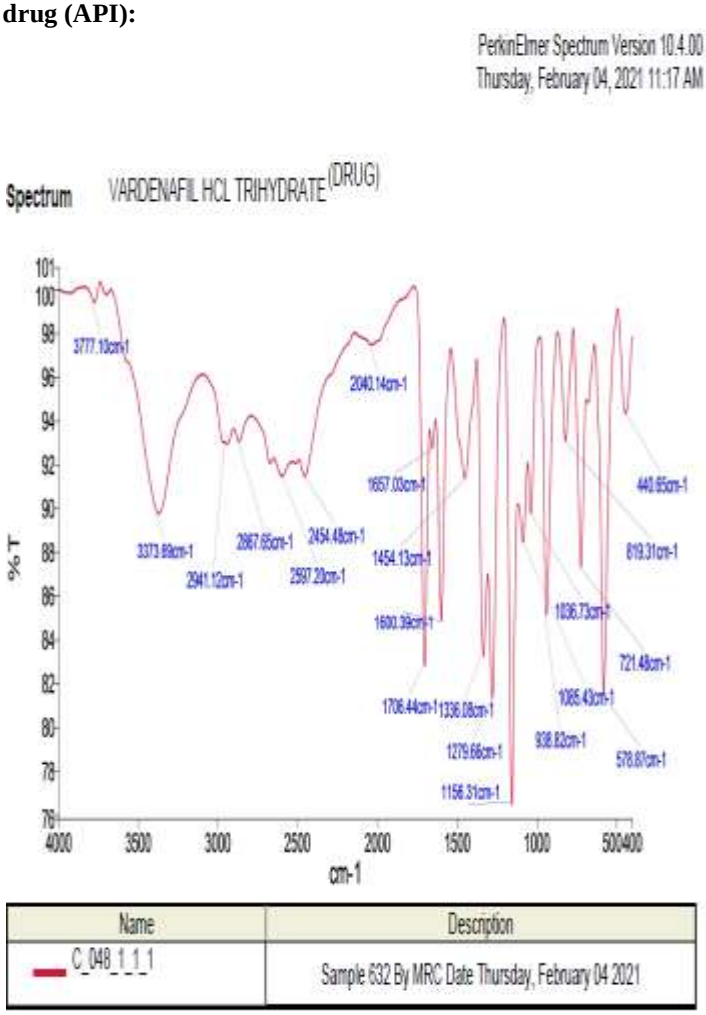

Figure 4 FTIR graph of drug sample

Melting Point of drug:

The melting range was found to be 218-230ºc through melting point apparatus.

Solubility profile of drug:

Solvent	Solubility
Acetonitrile : Water	Slightly Soluble
Ethanol	Soluble
Methanol	Soluble
Distilled water	Sparingly Soluble

Table 2 Solubility profile of sample drug

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 319-328 www.ijprajournal.com ISSN: 2249-7781

pH of drug:

The pH of drug was found to be 7.04 by using digital pH meter.

Spectrophotometric Estimation of Vardenafil HCl trihydrate in phosphate buffer 6.8 (Plotting of calibration curve):

Conc. (µ/ml)	Absorbance (at 214 nm)
0	0.000
5	0.143
10	0.285
15	0.46
20	0.58
25	0.681

Table 3 Absorbance of different conc.

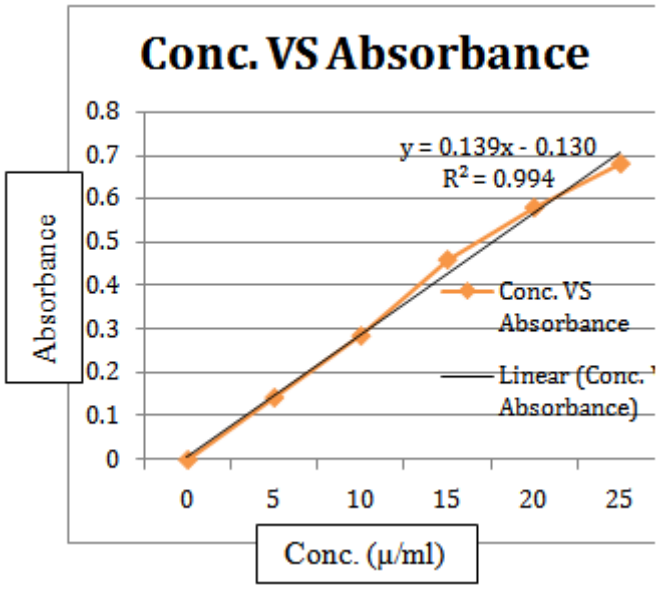

Figure 5 Calibration curve of drug sample

Evaluation parameters:

Parameters	Formulations			
	F1	**F2**	**F3**	**F4**
Tack test	Non tacky	Non tacky	Non tacky	Non tacky
Thickness test (mm)	0.10±0.03	0.12±0.06	0.14±0.04	0.16±0.07
Weight variation test (mg)	46.4±0.04	54.2±0.03	64.4±0.08	72.4±0.06
Folding endurance test(times)	125±5	135±5	195±5	215±5
Disintegration test time (sec)	51±0.218	52±0.241	54±0.507	59±0.586

International Journal of Pharmaceutical Research and Applications
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pH test	6.4±0.11	6.7±0.21	6.9±0.18	7.2±0.13
% Drug content test	96.1±0.03	95.8±0.02	98.3±0.08	97.8±0.05
% In-vitro dissolution test	84.34±0.03	92.12±0.04	96.42±0.02	80.26±0.06
% Moisture loss test	8.88±0.31	7.40±0.12	7.81±0.18	7.04±0.26
% Moisture content test	6.38±0.25	7.27±0.41	8.95±0.34	11.11±0.18
Tensile strength test(kg/mm²)	0.432±0.05	0.449±0.03	0.463±0.06	0.494±0.04
% Elongation test	6.17±0.195	6.21±0.338	6.48±0.125	6.75±0.413

Table 4 Results of evaluation tests performed (mean ± SD, n=3)

Percentage drug release profile of formulations:

Time (min)	**% Drug released**			
	F1	**F2**	**F3**	**F4**
1	18.41±0.03	25.13±0.07	29.31±0.06	12.83±0.05
2	51.1±0.05	59.41±0.01	65.14±0.02	45.27±0.03
3	60.22±0.01	67.24±0.08	77.63±0.05	56.31±0.01
4	76.6±0.03	85.53±0.03	85.45±0.01	65.48±0.08
5	84.34±0.04	92.12±0.04	96.42±0.03	80.26±0.03

Table 5 Drug release profile (mean± SD, n=3)

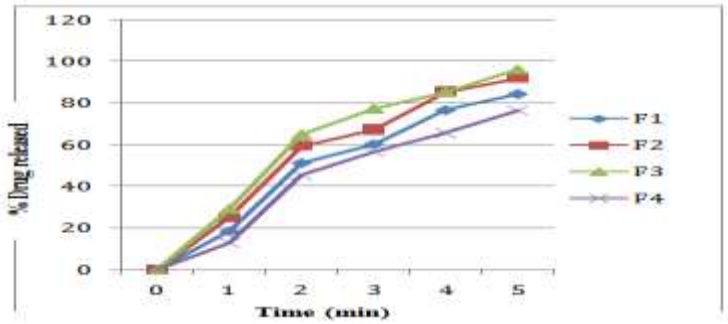

Figure 6 Percentage drug released on different time intervals (1-5 mins)

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SEM (Scanning electron microscopy):

From SEM test it was observed that the surface of dummy film (fig.7) was clear and the film of formulation F3 (fig.8) was also found to have a clear surface with minor scratches which shows the proper distribution of API within whole film.

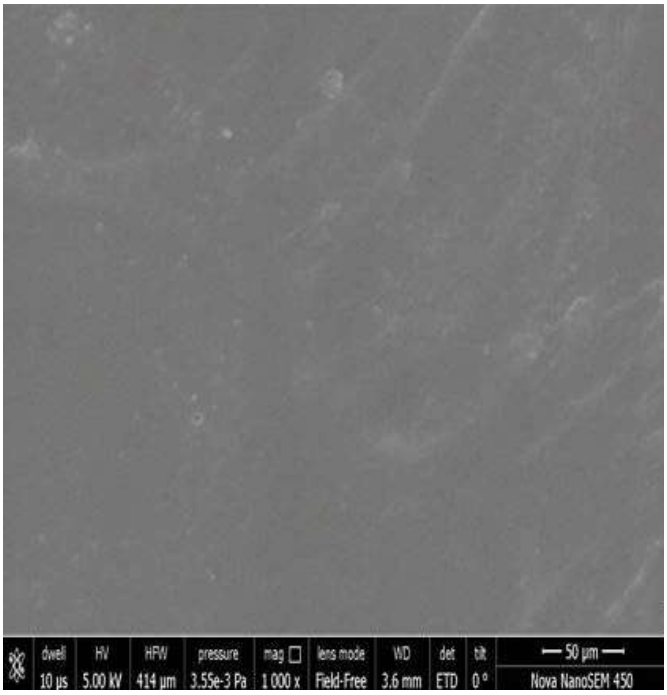

Figure 7 SEM image of dummy film (without API)

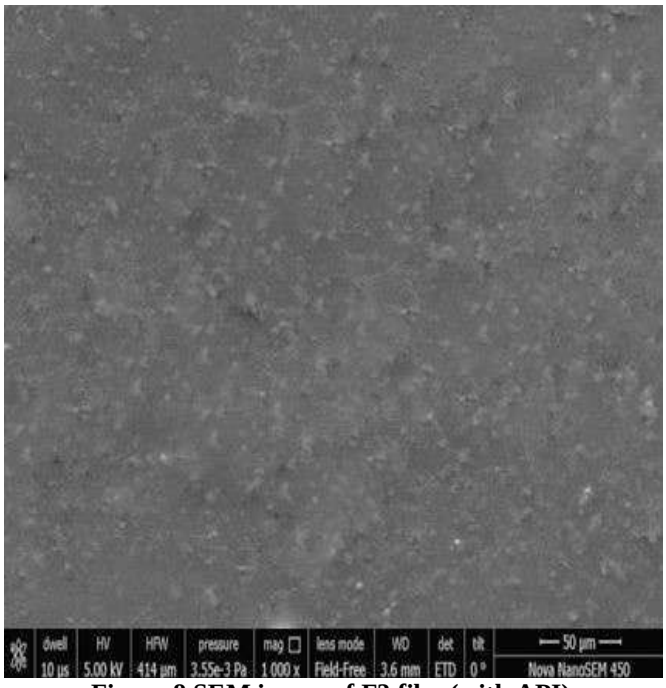

Figure 8 SEM image of F3 film (with API)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 319-328 www.ijprajournal.com ISSN: 2249-7781

Accelerated Stability Studies:

Time Interval	Parameters			
	Tack Test	Tensile Strength (kg/mm²)	Disintegration Time (sec)	% Drug Content
Initial	Non-tacky	0.463±0.06	54±0.507	98.3±0.08
After 10 days	Non-tacky	0.458±0.04	55±0.321	98.11±0.03
After 20 days	Non-tacky	0.450±0.07	55±0.142	97.8±0.04
After 30 days	Non-tacky	0.449±0.03	57±0.214	97.4±0.06
After 40 days	Non-tacky	0.446±0.08	59±0.417	96.4±0.02
After 50 days	Non-tacky	0.440±0.02	60±0.117	95.5±0.03
After 60 days	Non-tacky	0.437±0.04	62±0.318	95.1±0.07

Table 6 Accelerated stability studies of F3 (mean ± SD, n=3)

Time Interval	Parameters			
	Tack Test	Tensile Strength (kg/mm²)	Disintegration Time (sec)	% Drug Content
Initial	Non-tacky	0.494±0.04	59±0.586	97.8±0.05
After 10 days	Non-tacky	0.490±0.01	60±0.183	96.1±0.03
After 20 days	Non-tacky	0.484±0.07	63±0.208	95.5±0.06
After 30 days	Non-tacky	0.481±0.03	64±0.399	95.4±0.01
After 40 days	Non-tacky	0.477±0.05	66±0.513	94.6±0.03
After 50 days	Non-tacky	0.473±0.06	69±0.315	94.1±0.06
After 60 days	Non-tacky	0.470±0.08	70±0.481	93.8±0.03

Table 7 Accelerated stability studies of F4 (mean ± SD, n=3)

After performing accelerated stability studies, it was concluded that formulation F3 & F4 shows promising characteristic results with minor variations. Also there were no differences observed in the physical appearance, flexibility, drug content, disintegration time and tensile strength.

IV. DISCUSSION

Oral dispersible film of Vardenafil HCl trihydrate was formulated by solvent casting technique using polymer HPMC. The other ingredients used in the formulations had specific uses like Propylene glycol (Plasticizer), Methyl cellulose (thickening agent), Sucrose (Sweetener), Disodium EDTA (preservative) and Citric acid (Saliva stimulating agent). The formulations were further analysed for characteristic evaluation including thickness, folding endurance, tensile strength, % elongation, surface pH, disintegration time, drug content uniformity and drug release.

The thicknesses of the films were measured by using digital Vernier Calliper which varies from 0.10 to 0.16 mm. The formulated films shown constant distribution of the drug throughout

the film which was found within 95.8 to 98.3 % and surface pH of a film was found to be between 6.4 to 7.2. The weights of films were found to be between 46.4 mg to 72.4 mg. The disintegration times of films were found to be between 51 to 59 seconds and dissolution % was between 80.26 to 96.42%. F3 batch formulation was observed as the best formulation because the films of this batch shown characteristics of a ideal film as compared to all other batches.

V. CONCLUSION

Different formulations of oral dispersible films of Vardenafil HCl trihydrate were successfully formulated by solvent casting method using HPMC as a film forming agent, polyethylene glycol as plasticizer in different conc. and other excipients in constant quantity. Adequate and smooth textured films were obtained and throughout all batches F3 formulation were found to be the best formulation having all the promising parameters including mechanical, morphological and statistical. The overall result of this study was that the drug Vardenafil HCl trihydrate can be formulated in the form of oral dispersible films for better bioavailability and quick onset of action.

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