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Development characterisation and optimization of fast dissolving oral films of vardenafil using 3^2 full factorial design

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Abstract: *The current research in the field of drug delivery by which fast release can be achieved has been intensified .The Aim of the Present Study was to Develop, Characterize and Optimize Fast Dissolving Oral Films of Vardenafil by Solvent Casting Method .Based on Preliminary trials, HPMCE52V was selected as polymer, PEG 400 was selected as Plasticizer, Citric acid as Saliva Stimulating Agent, and Sucrose as sweetener respectively. A 3^2 Full Factorial design was employed for the Optimization to study the Effect of concentration of HPMCE52V (X_1)& Concentration of film former PEG 400(X_2) as Independent variables and to study the effect of Tensile strength(Y_1),Disintegration time(Y_2),In-vitro drug release in phosphate buffer PH 6.8at Q_5 min Y_3) as Dependent variables. Oral Fast Dissolving film of Batch F_1(HPMC E52V 100 mg; PEG 400 0.2ml) was identified as an Optimized Batch showing in –vitro Disintegration time 21.6 s,96.3% Drug Release at Q_5 min ,Satisfactory thickness, Strength % elongation ,Ease of Handling, Smooth Mouth Feel ,Excellent Over taste ,Even distribution of all Ingredients and stable film at specified conditions. It had a positive impact on disintegration time and drug release. Concluding that HPMCE52v,PEG 400 are used in combination to make palatable ,stable Oral Fast Dissolving Film of Vardenafil.*

Key Words: *Oro-dispersible, Optimize, Solvent Casting, Palatable, Stable*

1. INTRODUCTION: Oral route is the most preferred route of drug administration due to its Safety, Ease of administration and acceptability by its patients.

About 60% of the conventional dosage forms are available as the oral solid dosage forms. The low bioavailability, longer onset of action and dysphasia turned the manufacturer towards the parenteral and liquid dosage forms. But the liquid dosage forms (syrups, suspensions, emulsions) have the problem of accurate dosing. Parenterals are painful drug delivery systems, so they result in patient incompliance. Due to draw back effects of parental and liquid dosage forms, the most preferred route of drug administration is the oral route.

Oral drug delivery system includes conventional dosage form and immediate release dosage form. Conventional dosage forms like tablets, capsules, pills, powders solutions and aerosols are used in the treatment of acute or chronic diseases. Whereas, immediate release dosage forms are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release dosage forms may be provided by way of an appropriate pharmaceutical acceptable diluents or carrier.

When such a conventional dosage form is administrated the concentration of such drug in systemic circulation gradually rises to attend a therapeutic range and this concentration is maintained for some time and finally decreases to sub-therapeutic value rendering the drug pharmacologically inactive. Each individual drug has Maximum Safe concentration (MSC) and Minimum Effective Concentration (MEC).Fluctuations in plasma concentration may mean that drug levels may swing too high leading to toxic/side effects, alternatively drug may fall too low leading to lack of efficacy. Furthermore, the plasma drug concentration in a patient at particular time depends on the compliance with prescribed dosage interval.[2]

Special Features of Mouth Dissolving Films

- Thin and elegant film
- Available in various sizes and shapes.
- Non obstructive
- Excellent mucoadhesion
- Fast disintegration
- Rapid release.
- The drug should have pleasant taste.

The Ideal Characteristics of Drug to Be Selected:

- The drug to be incorporated should have low dose up to 40 mg
- The drugs with smaller and moderate molecular weight are preferable
- The drug should have good stability and solubility in water as in saliva.
- It should be partially unionized at the pH of oral caviy.
- It should have the ability to permeate oral mucosal tissue.

Advantages of Orally Fast Dissolving Films

- Administered without water anywhere and anytime.
- Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
- Oral dissolving films are flexible and portable in nature, so they provide ease in transportation during consumer handling and storage.
- Suitability for geriatric and pediatric patients who experience difficulty in swallowing mentally ill, the developmentally disable and the patients who are un-cooperative or are on reduced liquid intake plans or are nauseated.
- Beneficial in cases such as motion sickness, acute pain, sudden episodes of allergic attack or coughing where an ultra rapid onset of action is required.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So; it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bio-availability.
- As compared liquid formulations, precision is the administered dose is ensured from each strip of the film.
- The oral or buccal mucosa being highly vascularized drugs can be absorbed directly and enter in to the systemic circulation without undergoing first pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bio-availability of molecules that undergo first pass effect.
- The sublingual and buccal delivery of drugs via thin film has the potential to improve the onset of action, lower the dose and enhance the efficacy and safety profile of the medicament.
- Provide new business opportunity like product differentiation, product promotion and patent extension.

Advantages of Oral Fast Dissolving Films over Conventional Dosage Forms

- A fast dissolving film dissolves rapidly than other conventional dosage forms. These are less friable and easy to carry dosage form compared to commercialized orally fast disintegrating tablets, which need special packing.
- Likewise, a single dose of strip can be carried individually without requiring secondary container.
- In contrast to transdermal patch, the transdermal film is less associated with skin irritation due to less occlusive properties that improve the water vapor permeation through the skin and do not leave sticky sensation on the site of application.
- Conventional ophthalmic drug delivery systems such as eye drops, or solutions are commonly used but they are limited in their ability to provide high ocular drug bio-availability and sustained duration of action.opthalamic films can be used to improve drug delivery to the eye.
- It is very important to address the poor stability of liquid dosage forms, especially the aqueous formulations. Unlike fast dissolving films, there is need for great care during accurate measurement of the amount and shaking of the bottle every time before administration may contribute to less acceptance by the patients.

Disadvantages of Fast Dissolving Oral Films

- The disadvantage of oral thin film is that high dose cannot be incorporated in to the strip. The dose should be between 1-30 mg.
- Number of technical limitations with the use of film strip, like glass Petri plates cannot be used for casting. The thickness while casting the film.
- The other technical challenge with these dosage forms is that achieving dose uniformity.
- Packaging of films requires special equipments as it is difficult to pack.
- Eating and drinking may become restricted.
- Since oral fast dissolving films are hygroscopic in nature, so it must be kept in dry places.
- Oral fast dissolving films are moisture sensitive.

Major Limitations of Oral Fast dissolving films

- Use of oral fast dissolving films is limited largely due to low drug loading capacity for a less potent drug given at high dose. These are usually hygroscopic in nature. Thus, special precaution should be taken for their longer preservation.
- Combining more than one drug concomitantly is a very challenging task in oral formulation because both the dissolution rate and disintegration rate are hindered by the co-administration of drug in oral films.
- The difficulty to obtain a high degree of accuracy with respect to the amount of drug in individual unit dose of the film can lead to therapeutic failure, non-reproducible effects and sometimes toxic effects to the patient.
- Preparing oral film formulation is concerned with the issues of requiring excessive time for drying. It takes around one day for the complete drying at room temperature, which notably decreases' the rate of production of films, since it is not recommended to use hot air oven for thermo labile drugs, an alternative process of drying should be explored.
- Drugs with obnoxious odor cannot be administered.
- Fast dissolving oral films may be useful for eliminating side effects of a drug and reducing extensive metabolism caused by proteolytic enzymes.
- Oral fast dissolving films have shown the capabilities to improve the:
    - Onset of drug action.
    - Reduce the dose frequency.
    - Enhance the efficacy of drug.
    - To exhibit desirable features such as:
        - Drug loading capacity
        - Faster dissolution rate
        - To formulate non toxic, bio-compatible, bio-degradable film.

Properties of Ideal Oral Fast Dissolving Films

- An ideal film should be flexible, elastic and soft.
- It should have pleasant taste.
- It should also posses high stability and ease of handling.
- It must also posses' good bio-adhesive strength in order to be retained in the mouth for the desired duration of action.
- It should be adequately strong to withstand breakage due to stress from mouth movements.
- It should be convenient and portable without the need of water or measuring devices.
- It should posses' rapid onset of action and good bio –availability.
- Thickness ranges from 1-10 mm and its surface area ranges from 1-20cm.
- Its low dry tack allows for ease of application.
- 2mm thickness will take 5-10 sec to start its disintegration

2. LITERATURE REVIEW:

Vipul D.Prajapati., et al, (2017) developed the Pullulan based oral thin film formulation of Zolmitriptan using desired evaluations following optimization of process factors. The proposed formulation has the potential to improve

compliance and quick onset of action in migraine patients than the available tablets of zolmitriptan. This zolmitriptan loaded pullalan based OTF presents multiple competitive advantages over its marketed oral dosage forms such as ease of swallowing without water, very easy to formulate simplicity to handle, store and carry away.

K.M.Maheshwari, et al, (2014) developed the mouth dissolving films of Amlodipine Besylate to enhance convenience and compliance of elderly and pediatric patients for better therapeutic efficacy .HPMC &methyl cellulose were used as film formers along with film modifiers like PVP K30,&SLS as solubilizing agents were evaluated .the prepared mouth dissolving films were evaluated for in-vitro dissolution characteristics ,in-vitro disintegration time and their pshyicomechanical properties. All the prepared mouth dissolving films showed good mechanical properties like tensile strength, %elongation, folding endurance .mouth dissolving films were evaluated by means of FT-IR, SEM &XRD studies.

Tadese Mekonnen (2016) prepared the design and evaluation of fast dissolving buccal films containing tadalafil.in this research work low viscosity grade of hydroxyl propyl methyl cellulose (HPMC E5 and HPMC E15) were used as excipient due to their excellent film forming property and palatable taste .PEG 400 and propylene glycol were used as plasticizers .Tween 80 used as solubilizing agent. Aspartame and menthol .pine apple flavor used as taste masking agent and sweetener respectively.HPMC E15 was resulted in sticky film formation .concentration of PEG 400 and propylene glycol was optimized during pre-liminary studies. Formulation containing HPMC E5, HPMC E15, PEG 400 &Propylene glycol showed optimum performance against all other prepared formulations. The formulation was found to show significant improvement in terms of drug release as compared to tablet formulation.

3. OBJECTIVES / AIMS :

The aim of the present study was to Develop, Optimize and Characterize Fast Dissolving Oral films of Vardenafil using 3^2 Full Factorial Design to enhance its Solubility.

- Design and Optimize Fast Dissolving Oral Film by Solvent Casting Method using HPMC $E_5 2_v$ as polymer and PEG 400 as Plasticizer, Citric acid as saliva stimulating agent, Sucrose as Sweetener, Peppermint oil as Flavouring agent.
- Formulation of Fast Dissolving Oral films By Solvent Casting Method according to 3^2 Full Factorial Design
- To enhance Solubility &Dissolution rate by avoiding First Pass Metabolism.
- To make smooth mouth feel and stable film at specified conditions.

4. RESEARCH METHOD

4.1 Materials used

S. No	Materials	Company	Category
1	HPMC$E_5 2_v$	Oxford Laboratory Reagent	Polymer
2	PEG 400	S.D.Fine chemicals .Ltd Mumbai, India	Plasticizer
3	Citric acid	N.R chem. Laboratory	Saliva stimulating agent
4	Saccharin	S.D Fine Chemicals Ltd, Mumbai, India	Sweetening agent
5	Chloroform	S.D Fine chemicals .Ltd Mumbai, India	Solvent
6	Methanol	Oxford Laboratory Reagent	Solvent
7	Ethanol	Oxford Laboratory Reagent	Solvent
8	Peppermint oil	Oxford Laboratory Reagent	Flavoring agent

Table no: 4.1 list of chemicals

4.2 ANALYTICAL METHODS

4.2.1 Determination of λ_{max}

A drug solution 10µg/ml was taken from the prepared stock solution and was scanned in the range for 200-400nm by taking 0.1NHcl buffer solution as blank solution. The wavelength at which maximum absorption obtained was determined by using UV-visible double beam spectrophotometer.

Preparation of 0.1N HCl buffer

Accurately measured 8.5ml of concentrated HCl was taken in a 1000 ml volumetric flask and the volume was made up to 1000ml using distilled water and then kept aside for an hour and then used.

Calibration curve of Vardenafil in 0.1N HCl

Accurately weighed 100 mg of vardenafil was taken and dissolved in 0.1 N HCl and the volume was made up to 100 ml (1000µg/ml) (Stock Solution 1). From stock solution 1, 1 ml was pipette out and was diluted with 0.1 N HCl and the volume was made up to 100 ml (100µg/ml) (Stock Solution 2). From the stock solution 2, aliquots ranging from 0.5 – 2.5 ml were pipette out and diluted with 0.1 N HCl to get concentration range 5-25 µg/ml. The absorbance was measured at 270 nm against blank solution. Standard graph was plotted by keeping concentration on X-axis and obtained absorbance on Y-axis.

Preparation of 1.2 phosphate buffer solution

Place 8.5ml of concentrated hydrochloric acid in to the 1000ml volumetric flask and the volume was made up with de-mineralized water.

Calibration curve of vardenafil in 1.2 phosphate buffer

Accurately weighed 100 mg of vardenafil was taken and dissolved in 1.2phopshate buffer and the volume was made up to 100 ml (1000µg/ml) (Stock Solution 1). From stock solution 1, 1 ml was pipette out and was diluted with 1.2 phosphate buffer and the volume was made up to 100 ml (100µg/ml) (Stock Solution 2). From the stock solution 2, aliquots ranging from 0.5 – 2.5 ml were pipette out and diluted with 1.2 phosphate buffer to get concentration range 5-25 µg/ml. The absorbance was measured at 270 nm against blank solution. Standard graph was plotted by keeping concentration on X-axis and obtained absorbance on Y-axis.

Preparation of 0.2M NaOH

Place 8.0g of NaOH in to the 1000ml volumetric flask and the volume was made up with demineralized water.

Preparation of 0.2M Potassium Dihydrogen phosphate

Place 27.218 g of potassium dihydrogen phosphate in to the 1000ml volumetric flask and the volume was made up with de-mineralized water.

Preparation of 6.8 phosphate buffer solution

Place 50ml of 0.2M Potassium dihydrogen phosphate in a 200ml volumetric flask, add 22.4 ml of 0.2M NaOH and then add demineralized water to volume.

Calibration curve of vardenafil in 6.8 phosphate buffer solution

Accurately weighed 100 mg of vardenafil was taken and dissolved in 6.8 phosphate buffer and the volume was made up to 100 ml (1000µg/ml) (Stock Solution 1). From stock solution 1, 1 ml was pipette out and was diluted with 6.8 phosphate buffer and the volume was made up to 100 ml (100µg/ml) (Stock Solution 2). From the stock solution 2, aliquots ranging from 0.5 – 2.5 ml were pipette out and diluted with 6.8 phosphate buffer to get concentration range 5-25 µg/ml. The absorbance was measured at 270 nm against blank solution. Standard graph was plotted by keeping concentration on X-axis and obtained absorbance on Y-axis.

Preparation of 7.4 phosphate buffer solution

Place 50 ml of 0.2M potassium dihydrogen phosphate in a 200 ml volumetric flask and add 39.04 ml of NaOH and then add de-mineralized water to volume.

Calibration curve of Vardenafil in 7.4 phosphate buffer solution

Accurately weighed 100 mg of Vardenafil was taken and dissolved in 7.4 phosphate buffer and the volume was made up to 100 ml (1000µg/ml) (Stock Solution 1). From stock solution 1, 1 ml was pipette out and was diluted with 7.4 phosphate buffer and the volume was made up to 100 ml (100µg/ml) (Stock Solution 2). From the stock solution 2, aliquots ranging from 0.5 – 2.5 ml were pipette out and diluted with 6.8 phosphate buffer to get concentration range 5-25 µg/ml. The absorbance was measured at 270 nm against blank solution. Standard graph was plotted by keeping concentration on X-axis and obtained absorbance on Y-axis.

4.3 SOLID STATECHARACTERIZATION OF FILMS

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR is used to compare the physical properties of the mixtures with those of plain drug. Samples were mixed uniformly with 100 mg of KBr powder and were compacted under vacuum at a pressure of about 12 psi for 3 minutes. The obtained disc was mounted in the (Agilent Cary 630 FTIR) holder of the FTIR spectrophotometer and the spectrum was used for the analysis in the frequency range between 4000 and 400cm-1 and resolution. The same procedure was followed for the drug and excipient mixture and is compared for any difference between the peaks.

Differential Scanning Calorimetry (DSC) Studies

Powdered sample of vardenafil were hermetically sealed in aluminum pans and heated at a constant rate of 5°C over a temperature range of 0-300°C.thermogram of samples was obtained using differential scanning calorimeter(Chip-DSC 10, Linseis).thermal analysis data were recorded using universal software. Indium standard was used to calibrate the DSC temperature and enthalpy scale .Alumimium pan with lid was used for all samples. The powder samples were weighed in an aluminum pan then sealed with pin holes and analyzed. An empty aluminum pan was used as a reference.

MORPHOLOGICAL ANALYSIS OF FILMS

Scanning Electron Microscopy (SEM) Studies

Scanning Electron Microscopy was conducted to characterize the surface morphology of the particles. The samples were mounted on alumina stubs, coated with gold in HUS-5GB vacuum evaporator. Then the samples were observed in JSM-7800F Schottky Field Emission Scanning Electron Microscope and examined at an excitation of voltage of 5 Kv

PRELIMINARY TRIALS:

Selection of Polymers:
Polymers such as HPMC E_52_v, and plasticizer were tried for the preparation of fast dissolving oro-dispersable films (FDF). HPMC E_52_v did not show good results at 40-50%concentration (the film was not easily peelable) whereas the films of HPMC in the range of 35-30% concentration also did not give good results (film weight is more). The concentration of HPMC $E_5$2V in the range of 25% did not give the good results (the film was sticky in nature). Many trials were done on different polymers like HPMC 15cps,(the weight is very less) HPMC LV(due to its low viscosity film was sensitive in nature) where as HPMC K_{100}.the weight of film is very thick).by using polyvinyl alcohol as p. By considering all the above preliminary studies the percentages between HPMC $E_5$2V 10- 20% was selected for the formulation of Films.

Selection of Plasticizers:
Selection of best compatible plasticizer is essential for the formulation of the films .Various plasticizers were selected and trials were done it was observed that from the varieties of plasticizers· Like namely Glycerin, Propylene glycol, Polyethylene glycols are commonly used plasticizers for the formulations of films. Propylene glycol below 15% did not show film properties as was tested by folding endurance of the film, where as Polyethylene glycol (PEG 200) did not give good results as was tested by Thickness. , polyethylene glycol (PEG300) as they formed visually superior transparent films and had low water vapor permeation rate..By all the above preliminary trials it was concluded that

polyethylene glycol (PEG400) are preferred to make stable ,flexible with desired mechanical strength it was identified as the best one for making flexible with required mechanical strength.

Selection of the Sweetener:

To identify the compatibility and influence of the sweeteners on palatability of OTFs like Aspartame, Sucralose Manitol, and Sodium saccharine. Sucralose was used as semi-synthetic sweetener. Mannitol is not preferred as it not crystalloid out when films are dried. Sucralose is selected because it is non toxic non carcinogenic and highly stable having high sweetening agent and universal accepted as sweetener for varieties of food and pharmaceutical products.

Selection of Saliva Stimulating Agent:

These agents are used to increase the secretions of saliva so that the oral film may dissolve are disintegrate in the oral faster in the oral cavity. Citric acid, lactic acid, mallic acid, ascorbic acid are the saliva stimulating agents. The acids which are used in the preparation of food are generally used as saliva stimulating agents. Among all the stimulating agents citric acid is mostly preferred.

Selection of the Flavouring Agent:

Flavouring agents are those ingredients which impart flavour to any of the formulation. Any US-FDA flavour can be added for the formulation. Flavouring agents should be compatible with the drugs and other excipients. Among all the flavouring agents pippermintoil is selected.

FACORIAL DESIGN [2]:

To get an optimized oral fast dissolving film a 3^2 factorial design (two factor three levels) factorial design was applied. Amount of HPMC(X_1 mg) and amount of PEG 400 (X_2).were selected as independent variables. Tensile strength (Y_1) Disintegration time (Y_2) and drug release (Y_3) in phosphate buffer pH 6.8 were used as responses.

Independent variables	Level		
	-1(low)	0(medium)	+1(high)
X_1 : Amount of HPMC$E_5 2_v$ (mg)	100	150	200
X_2 : Amount of PEG400 (ml)	100	150	200
Dependent variables			
Y_1 : Tensile strength			
Y_2 : Disintegration time			
Y_3 : Drug release			

Table 4.2 : Independent and Dependent variables used in 3^2 Factorial Design

Formulation	X_1	X_2
F_1	+1	+1
F_2	0	+1
F_3	- 1	+1
F_4	+1	-1
F_5	0	-1
F_6	-1	-1
F_7	+1	0
F_8	0	0
F_9	-1	0

Table 4.3: Coded Table for 3^2 Factorial Design

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Vardenafil (mg)	10	10	10	10	10	10	10	10	10
HPMC $E_5 2_V$ (mg)	100	150	200	100	150	200	100	150	200
PEG 400 (mg)	0.2	0.4	0.6	0.2	0.4	0.6	0.2	0.4	0.6

Citric acid (mg)	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Sucrose (mg)	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Ethanol (ml)	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Methanol (ml)	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Chloroform (ml)	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**

Table 4.4: Formulation of oral fast dissolving film of Vardenafil according to 3^2 Experimental Design

Method of preparation of Oral Fast Dissolving Films of Vardenafil

Among several techniques of film manufacturing, Solvent Casting Method is Feasible, Preferable and widely used technique due to straight forward manufacturing process and low cost of manufacturing process, and low cost of processing. The manufacturing method of oral thin films with the solvent casting method consist of following steps

- Selection of Solvent System.
- Preparation of polymeric solution or suspension
- Casting of the polymeric solution or suspension
- Drying of the casting solution (air drying at room temperature)
- Peeling cutting and packaging of the prepared film

PROCEDURE

The oral thin films were prepared by the method of solvent casting method. An oval shaped glass petri plate is used as substrate for casting of the film. Firstly the weighed quantities of polymer HPMC $E_5 2_V$ and plasticizer PEG 400 were dispersed in a solution. An accurately weighed quantity of vardenafil was incorporated to the above solution and the solvents like methanol, ethanol, and chloroform were added in equal proportions. The solution was kept on a magnetic stirrer with continuous stirring for 30 minutes at 500rpm. The solution was mixed occasionally to get a homogenous solution and saliva stimulating agent, sweetening agents were added. Then the solution was subjected to sonication in bath sonicator to remove the air bubbles. Then the solution was casted on a Glass Petri plate and subjected for air drying for 24 hrs. The film was carefully removed from the Petri dish, checked for any imperfections and cut into the required size to deliver the equivalent dose (2 x 2 cm2) per film. The samples were stored in desiccators until further analysis. Film samples with air bubbles, cuts or imperfections were excluded from the study.

Characterization of Fast Dissolving Films

Weight Variation Test

2 × 2 cm2 film was cut at three different places in the cast film. The weight of each film strip was taken and then weight variation observed.

Thickness : All the batches were evaluated for thickness by using screw gauze or digital vernier caliper. Three readings from all the batches were taken and mean thickness was evaluated. This is helpful in determination of uniformity in the thickness of the film**.**

Folding Endurance

Folding endurance is determined by folding the films repeatedly at same place until it breaks. The number of time the film is folded without breaking is computed as folding endurance value**.**

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Tensile strength

Tensile strength is the maximum stress applied to a point at which the films specimen breaks. This test performed to check brittleness of FDFs and there won't be any damage while handling or during transportation**.** It is calculated by the formula

$$\text{Tensile strength} = \frac{\text{Force at break (gm)}}{\text{Initial cross sectional area of th film cm2}}$$

Percentage Elongation

When stress is applied, a film sample stretches and this is referred to as strains. Generally elongation of film increases as concentration of plasticizer increases.

$$\text{Percentage elongation} = \frac{\text{Increase in Lengh}}{\text{Original length}} \times 100$$

Surface pH of Film

The surface pH of Mouth dissolving film is determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to keep the surface pH as close to neutral as possible. Film is slightly wet with the help of water. The pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed on three films of each formulation and mean ± S.D calculated.

Uniformity of Drug Content

Drug content of all batches was determined by UV-Spectrophotometric method. For this 2x2 cm2 film from the each film was cut and added into 100 ml volumetric flask containing methanol, Sonicate and stir for 10 minutes. Make up the volume up to 100 ml. From this solution 5 ml was withdrawn and added into 50 ml volumetric flask and finally volume was made to 50 ml with methanol. The solution was filtered and absorbance was recorded at 270nm. Drug content was calculated by using standard curve of drug.

In vitro Disintegration Time

In vitro disintegration time is determined visually. Disintegration time provides an indication about the disintegration characteristics of the film. Require size of film (4 cm2) of selected formulations was placed in a glass Petri dish containing 10 ml of distilled water and swirling every 10 sec. The time was noted down till film was completely converted into small pieces. Test was performed 3 times on each formulation

Percentage Moisture Absorption (PMA).

The PMA test was carried out to check the physical stability of the mouth dissolving film at high humid conditions. Three films were taken, weighed accurately and placed in desiccators containing saturated solution of aluminum chloride, keeping the humidity inside the desiccators at 79.5 %. After 72 hours the films were removed, weighed and percentage moisture absorption was calculated by using the following formulae.

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

Percentage moisture loss (PML)

Percentage moisture loss was calculated to check the integrity of films at dry condition. Three 4cm square films was cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. The percentage moisture loss was calculated by using.

$$\text{PML} = \frac{(Initial\ Weight - Fianl\ weight}{initial\ weight} \times 100$$

In vitro Dissolution Studies

The in vitro dissolution study was carried out in USP paddle apparatus. Accurately weighed MDF equivalent to 10 mg of Vardenafil) were introduced in the dissolution media. The dissolution was carried out in 200 ml of phosphate buffer solution (pH 6.8), for 10 min at 37 ± 0.5°C at a speed of 50 rpm and subsequently, the dissolution media was replaced with equal volume of the respective dissolution medium. At predetermined time intervals, 5 ml samples were withdrawn. Every time the sample withdrawn was replaced by fresh dissolution media maintained at the same temperature. The samples removed were filtered and analyzed spectrophotometrically at 270nm.

Ex-vivo Permeation Studies

Ex-vivo permeation studies were carried out through goat oral mucosa using modified Franz diffusion cell .This system consists of a donor chamber and receptor cell. Jacket and sampling port. The buffer was warmed with the in built heater and then assembly was set thermostatically at 37°c. A Teflon coated mini magnetic bead was placed in the receptor compartment for agitating the contained vehicle at 50rpm. The receptor compartment was filled with vehicle containing phosphate buffer pH6.8 receptor fluid was sonicated to remove the air bubbles and equilibrated at 37°C before placing the receptor component. The mucosa was mounted between the donor and receptor compartment. The receptor component was filled with 5ml of isotonic phosphate buffer of pH6.8 buffer magnetic bead was placed and rotations were 100rpm was maintained. 2x2 film was placed in intimate contact with the mucosal surface of the membrane for every 5mints 1ml sample was withdrawn and replaced with fresh phosphate buffer medium at suitable time intervals of 5,10,15,20,25,30min respectively

5. RESULT & DISCUSSION

PRE-FORMULATION STUDIES

S.No	API CHARACTERISATION	RESULTS
1.	Drug	Vardenafil
2.	Physical Appearance	White to white –off crystalline solid
3.	Odor	Characteristic odor
4.	Boiling point	214-216°c
5.	Melting point	692.2°c at 760mm of Hg

Table 5.1: Preformulation studies

The drug Vardenafil was white to white off crystalline solid in texture. It has characteristic Odour.and the boiling point of Vardenafil was found to be 214-215°c and melting point was found to be 692.2°c at 760mm of Hg.

SOLUBILITY STUDIES

S.No	TYPE OF SOLVENT	LEVEL OF SOLUBILITY
1	Water	Slightly soluble
2	Methanol	Freely soluble
3	Ethanol	Soluble
4	DMSO	Soluble
5	Chloroform	Soluble
6	6.8 phosphate buffer	Sparingly soluble
7	7.4 phosphate buffer	Sparingly soluble

Table 5.2: Solubility Studies of Vardenafil

The drug Vardenafil was found to be freely soluble in Methanol, Soluble in Ethanol, DMSO, Chloroform, Slightly soluble in Water, and Sparingly Soluble in 6.8 phosphate buffer and 7.4 Phosphate Buffer.

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DETERMINATION OF LAMBDA MAX OF VARDENAFIL

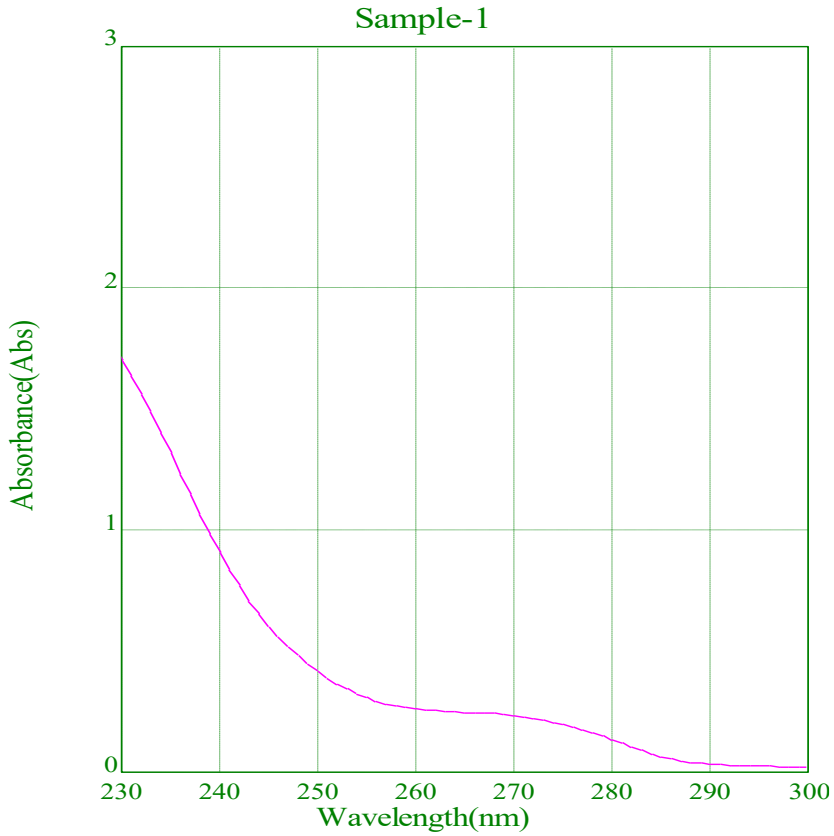

Fig 5.1: determination of wavelength

Drug showed maximum absorbance in 6.8 phosphate buffer and hence 6.8 Phosphate buffer was used as solvent. Drug solution of 10µg/ml was scanned over the range of 200-400nm in UV region. It was observed that the drug showed maximum absorbance at 270 nm and hence 270nm was selected as the detection wavelength. .

Standard Calibration Curve

From the standard stock solution (1000µg/ml).Appropriate aliquots were transferred to series of 10ml volumetric flasks and made up to 10 ml with desired solvents so as to get concentration of 5, 10, 15, 20…or 2,4,6,8…..µg/ml.The absorbance of the solution were measured at 270 nm for Vardenafil .This procedure was performed in triplicate to validate calibration curve. Calibration curve was plotted in different media like 6.8 phosphate buffer, 7.4 phosphate buffer, 1.2 phosphate buffer & 0.1NHcl.

Standard Curve of Vardenafil in 6.8 phosphate buffer:

S.no	Concentration (µg/ml)	Absorbance
1.	2	0.033
2.	4	0.235
3.	6	0.3423
4.	8	0.5026
5.	10	0.6881
6.	12	0.8334

Table 5.3: Standard plot of Vardenafil in pH 6.8 phosphate buffer

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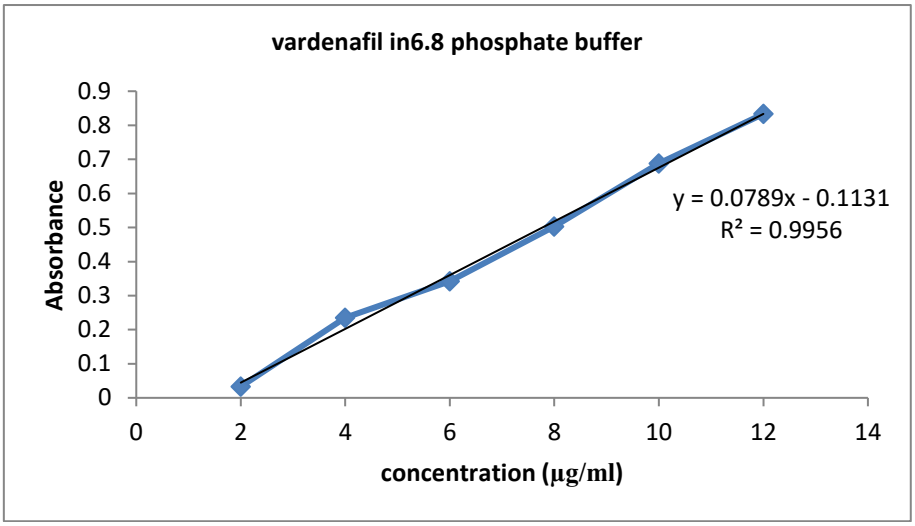

Fig 5.2: Standard Plot of Vardenafil in 6.8 phosphate buffer

Standard Curve of Vardenafil in 7.4 phosphate buffer

S.no	Concentration (µg/ml)	Absorbance
1.	2	0.0244
2.	4	0.0351
3.	6	0.0587
4.	8	0.0801
5.	10	0.0927
6.	12	0.1123

Table 5.4: Standard plot of Vardenafil in 7.4 phosphate buffer

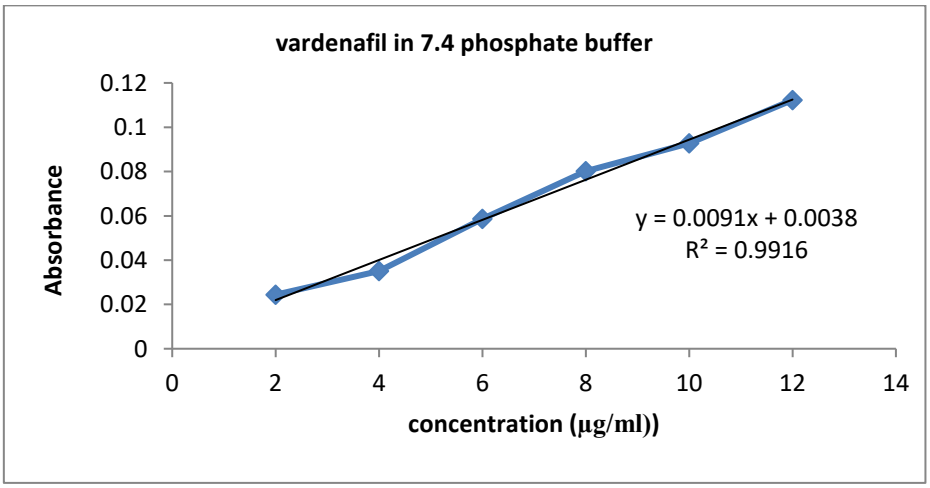

Fig 5.3: Standard Plot of Vardenafil in 7.4 phosphate buffer.

Standard Curve of Vardenafil in 0.1NHcl buffer

S.no	Concentration (µg/ml)	Absorbance
1.	2	0.076
2.	4	0.153
3.	6	0.246
4.	8	0.321
5.	10	0.432
6.	12	0.525

Table 5.4: Standard plot of Vardenafil in 0.1N Hcl buffer

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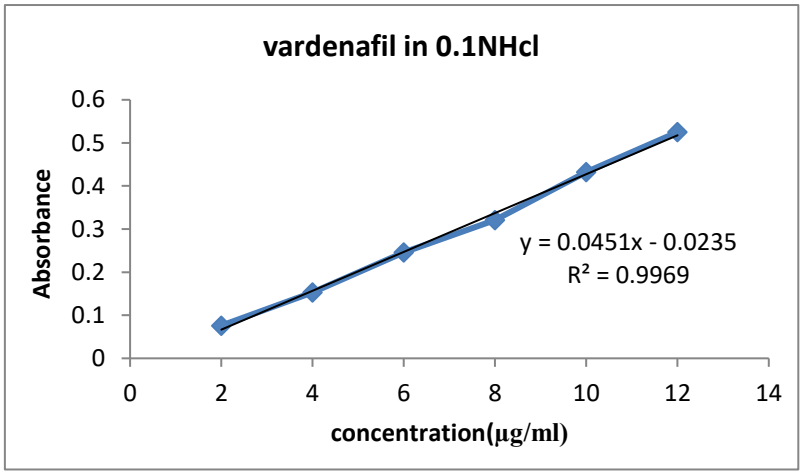

Fig 5.5: Standard Plot of Vardenafil in 0.1N Hcl buffer

Standard Curve of Vardenafil in 1.2 phosphate buffer

S.no	Concentration (µg/ml)	Absorbance
1.	2	0.0105
2.	4	0.0285
3.	6	0.0432
4.	8	0.0589
5.	10	0.0687
6.	12	0.0795

Table 5.5: standard plot of vardenafil in 1.2 phosphate buffer

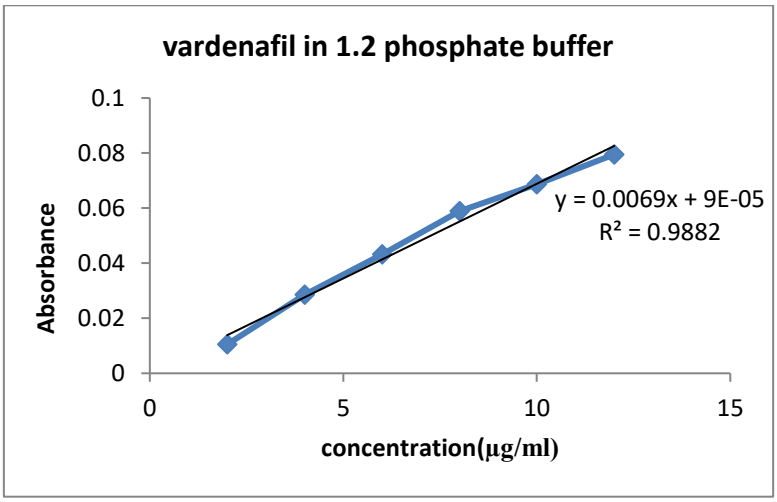

Fig 5.5: Standard Plot of Vardenafil in 1.2 phosphate buffer.

SOLID STATE CHARACTERIZATION OF ORAL FAST DISSOLVING FILMS

Fourier Transform Infrared Spectroscopic studies (FT-IR)

Compatibility studies were performed using FTIR spectrophotometer. The FTIR spectrum of pure drug and its physical mixtures were studied. The peaks obtained in the spectra of physical mixtures of drug were correlated with that of pure drug. From the FTIR spectrum, it was concluded that there was no significant shift the drug, exhibited the peaks at 2900 cm-1 for CH aromatic stretching, 1730 cm-1 stretch for carbonyl group, 3330 cm-1 stretch for NH2, 1100 – 1300 cm-1 stretch for SO2. Similar spectrum peak points were observed in all the formulations. This clearly indicates that there is no drug excipient interaction.

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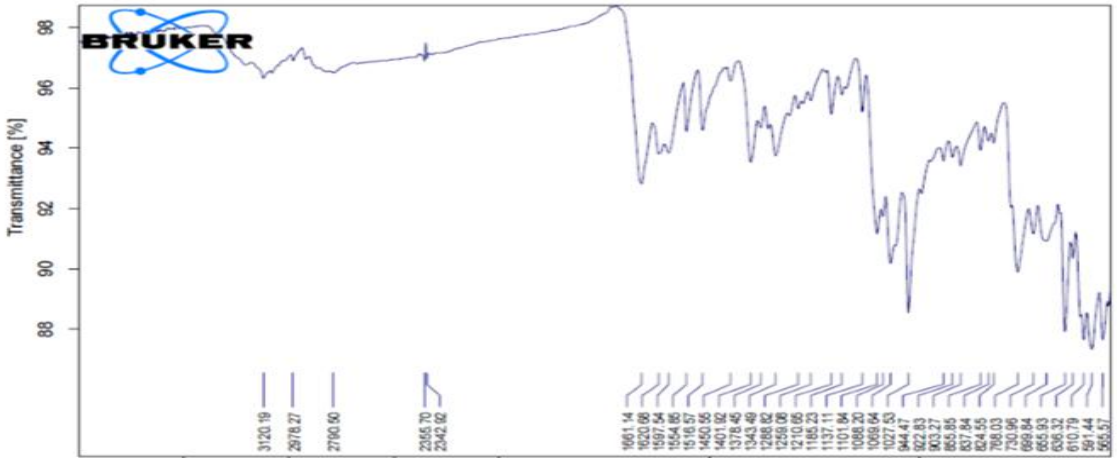

Fig 5.6: FT-IR spectra of pure drug

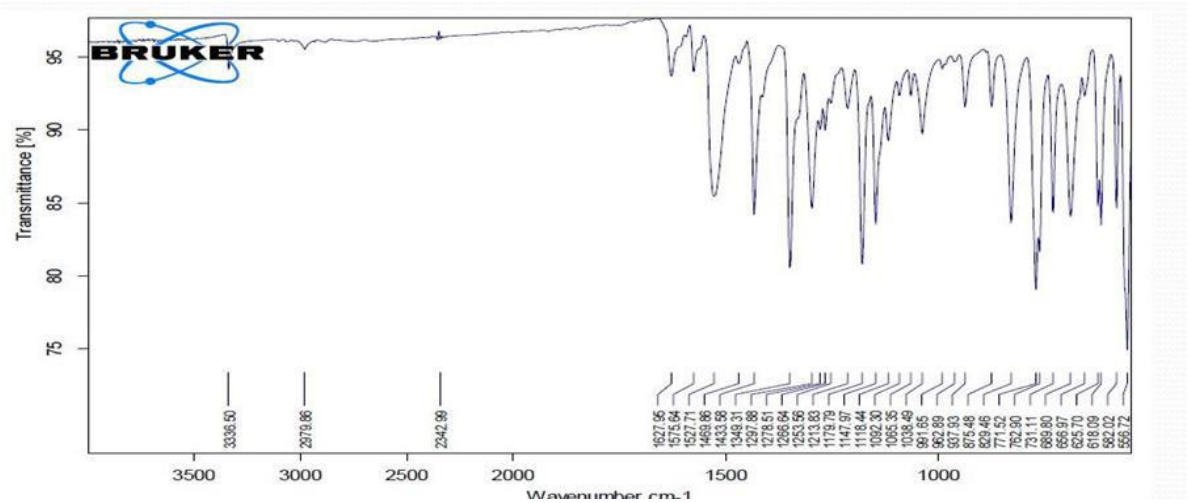

Fig 5.7: FT-IR Spectra of Optimized Formulation

Differential Scanning Calorimetry (DSC)

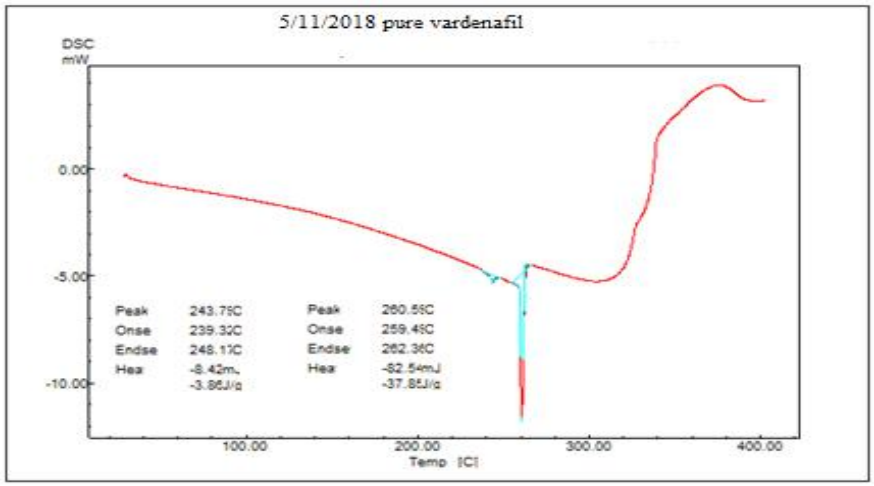

Fig 5.8: DSC of pure Vardenafil

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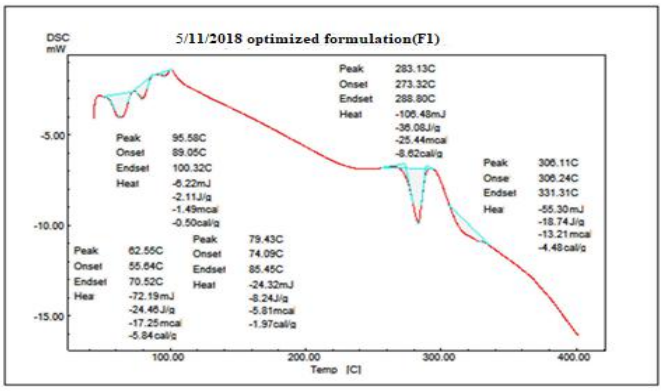

Fig 5.9: DSC of optimized formulation (F1)

Inference

Figure shows the DSC curve of Vardenafil, very strong and sharp endothermic peaks appear at 218.93 °C indicating that the drug is crystalline. The presence of vardenafil peak (in Fig) indicates that there was no interaction of drug with its excipients.

MORPHOLOGICAL ANALYSIS OF FILMS

Scanning Electron Microscopy (SEM)

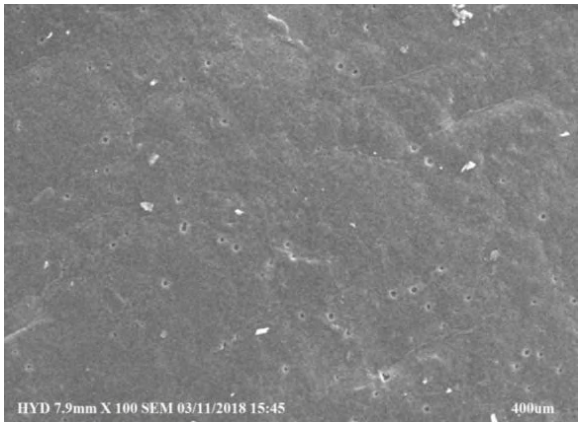

Fig 5.10: SEM image of Vardenafil

Fig 5.11: SEM image of Optimized Formulation

Inference

The surface morphology as shown in Figure 5.8 & 5.9 using scanning electron microscopy of the optimized orally dissolving strip formulation of Vardenafil depicted smooth surface with some little pores, which is an indication of uniform distribution of drug particles.

EXPERIMENTAL DESIGN RESULTS:

An experimental plan layout of a 3^2 factorial design is applied and independent variables were taken as (X1) Amount of polymer HPMCE52V and(X2) Amount of PEG 400.Dependent variables were taken as (Y_1) Disintegration time& (Y_2) Tensile strength.

ANOVA for Quadratic model

Response 1: DT

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	39.20	5	7.84	33.55	0.0078	significant
A-HPMC E52V	0.6667	1	0.6667	2.85	0.1898	
B-PEG 400	6.41	1	6.41	27.41	0.0136	
AB	6.25	1	6.25	26.74	0.0140	
A^2	3.21	1	3.21	13.73	0.0341	
B^2	22.67	1	22.67	97.00	0.0022	
Residual	0.7011	3	0.2337			
Cor Total	39.90	8				

Table 5.6 : ANOVA Table for Disintegration Time

ANOVA for Quadratic model

Response 2: Tensile strength

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2.74	5	0.5479	0.8942	0.5754	not significant
A-HPMC E52V	0.0726	1	0.0726	0.1185	0.7534	
B-PEG 400	0.0002	1	0.0002	0.0002	0.9885	
AB	0.5776	1	0.5776	0.9427	0.4032	
A^2	0.6272	1	0.6272	1.02	0.3862	
B^2	1.46	1	1.46	2.39	0.2201	
Residual	1.84	3	0.6127			
Cor Total	4.58	8				

Table 5.7 : ANOVA Table for Tensile Strength

ANOVA for Quadratic model

Response 3: Drug release

Source	Sum of squares	DF	Mean square	F-value	P-value	
model	435.73	2	217.86	1.05	0.4064	significant
HPMCE52V	167.06	1	167.06	0.8053	0.4041	significant
PEG 400	268.67	1	268.67	1.30	0.2985	significant
Residual	1244.70	6	207.45			
Cor total	1680.43	8				

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Table 5.8: ANOVA Table for drug release

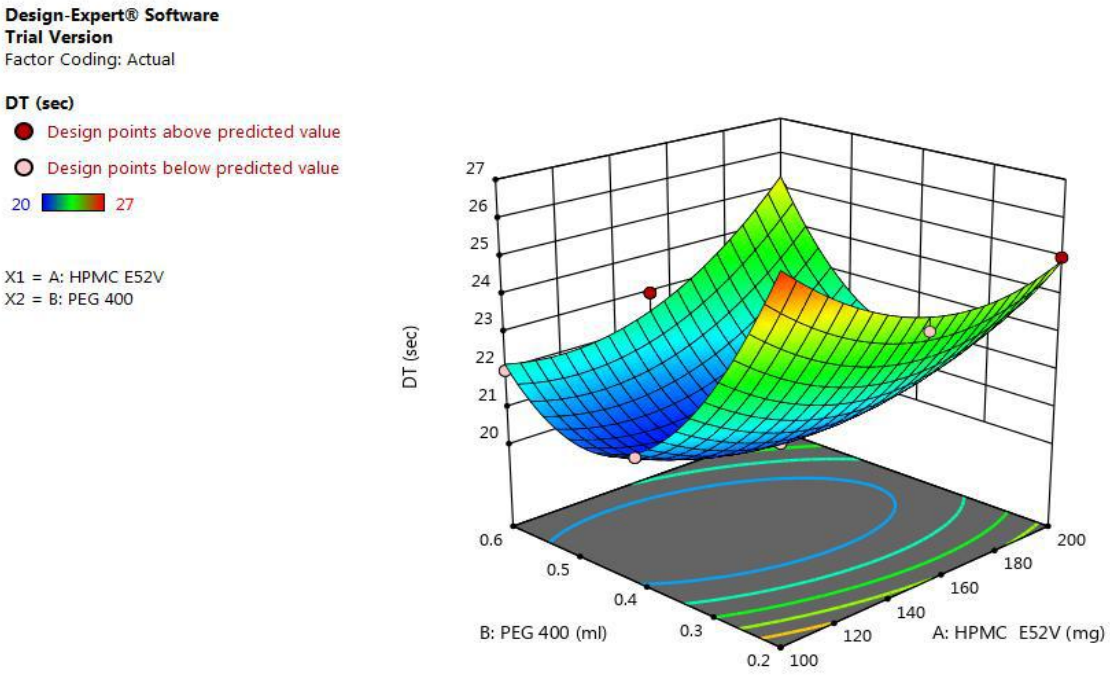

Fig 5.12: 3 Dimensional Surface Response Plots showing the Effect of amount of HPMC (X_1) and PEG 400(X_2) on Response Disintegration time(Y_1)

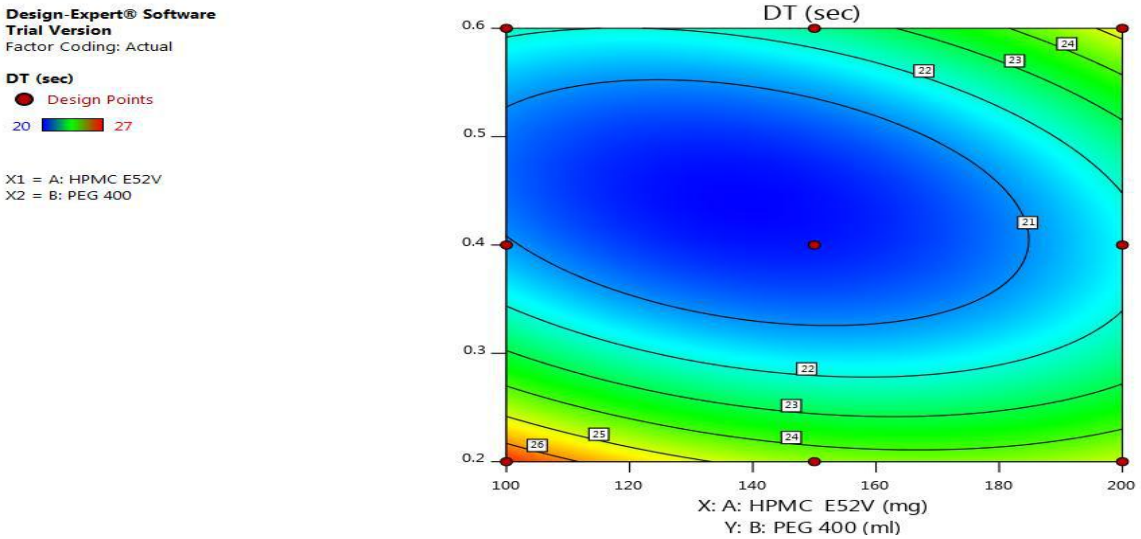

Fig 5.13: Contour plots showing the Effect of amount of HPMC(X_1) and PEG 400(X_2) on Response Disintegration time (Y_1)

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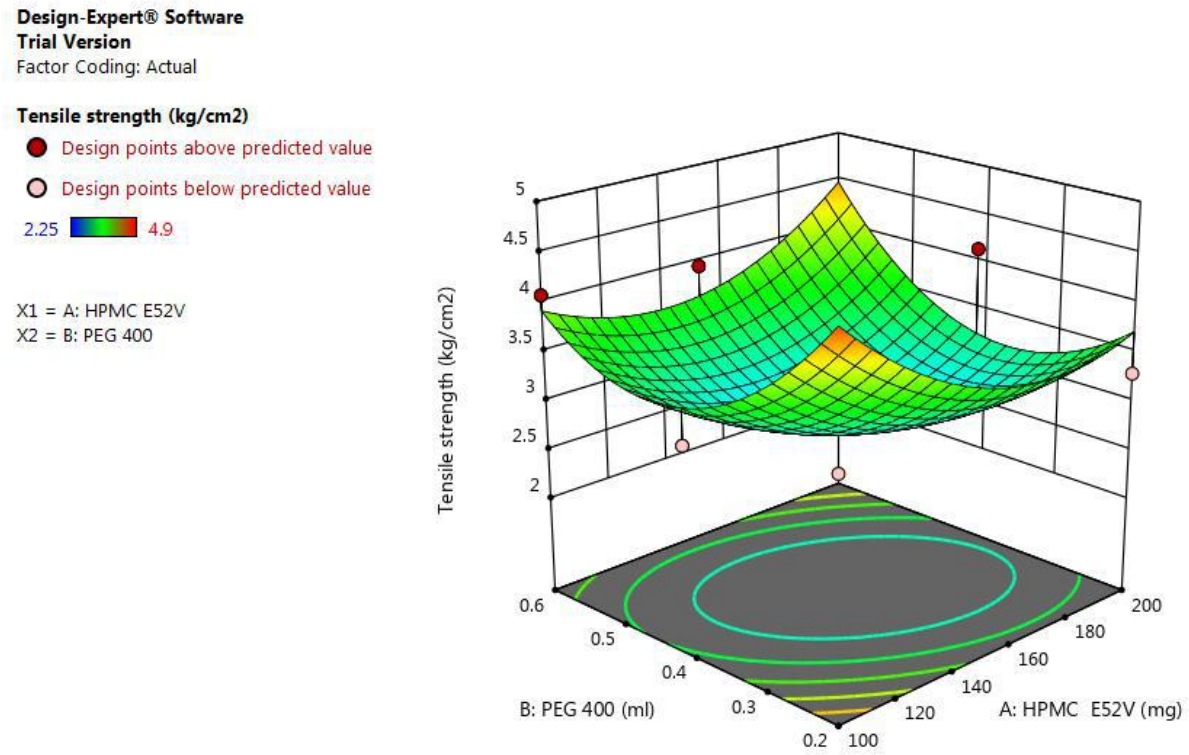

Fig 5.14: 3 Dimensional Surface Response Plots showing the effect of Amount of HPMC (X_1) and PEG 400(X_2) on Response Tensile strength(Y_2)

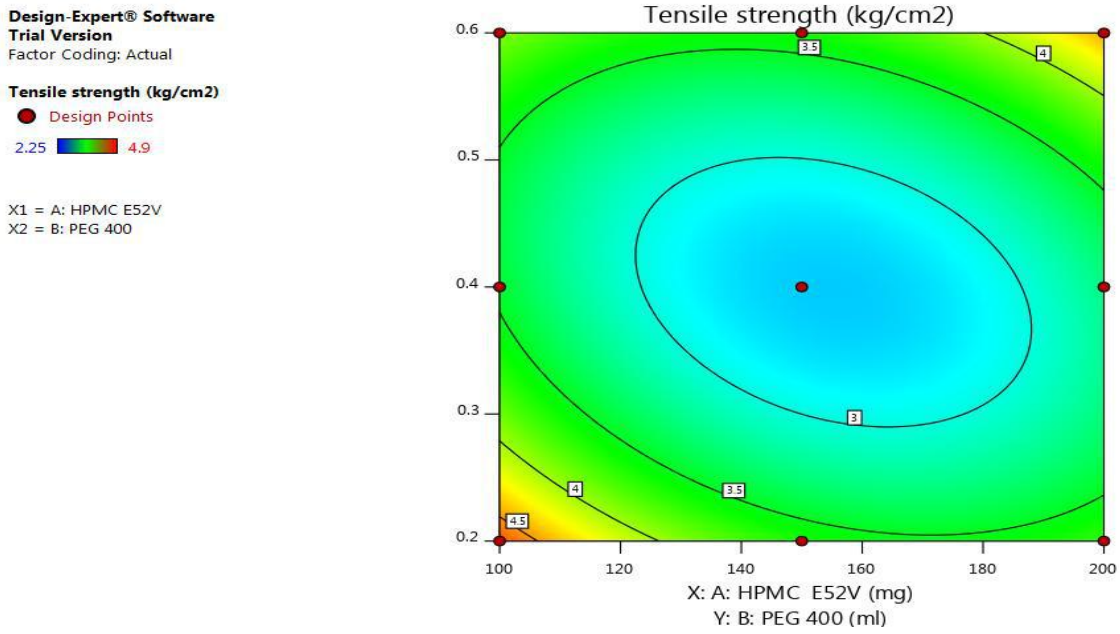

Fig 5.15: Contour Plots Showing the Effect of Amount of HPMC(X_1) and PEG 400(X_2) on response Tensile Strength(Y_2)

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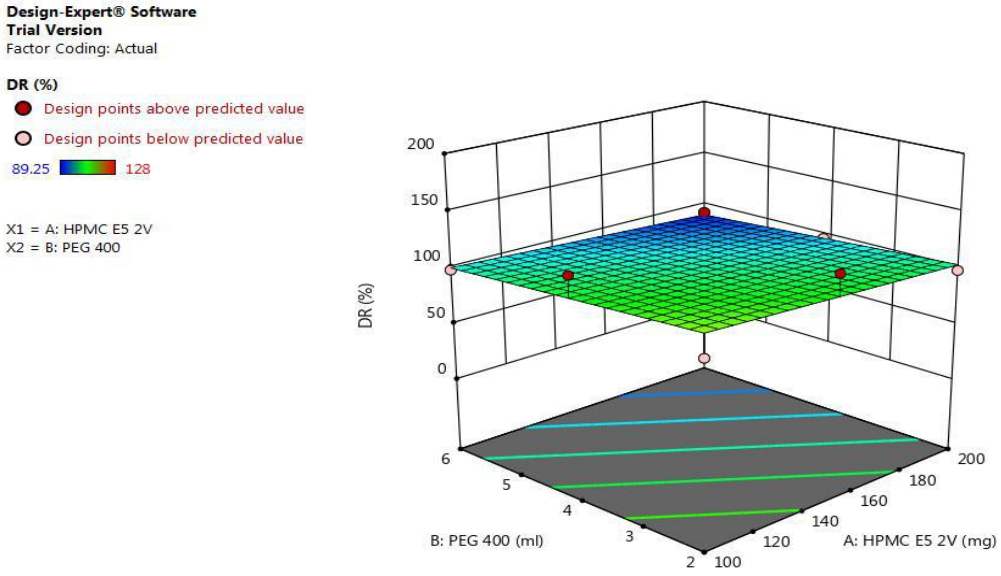

Fig 5.16: 3 dimensional surface plot showing the effect of amount of HPMC(X_1) and PEG 400(X_2) on response Drug Release

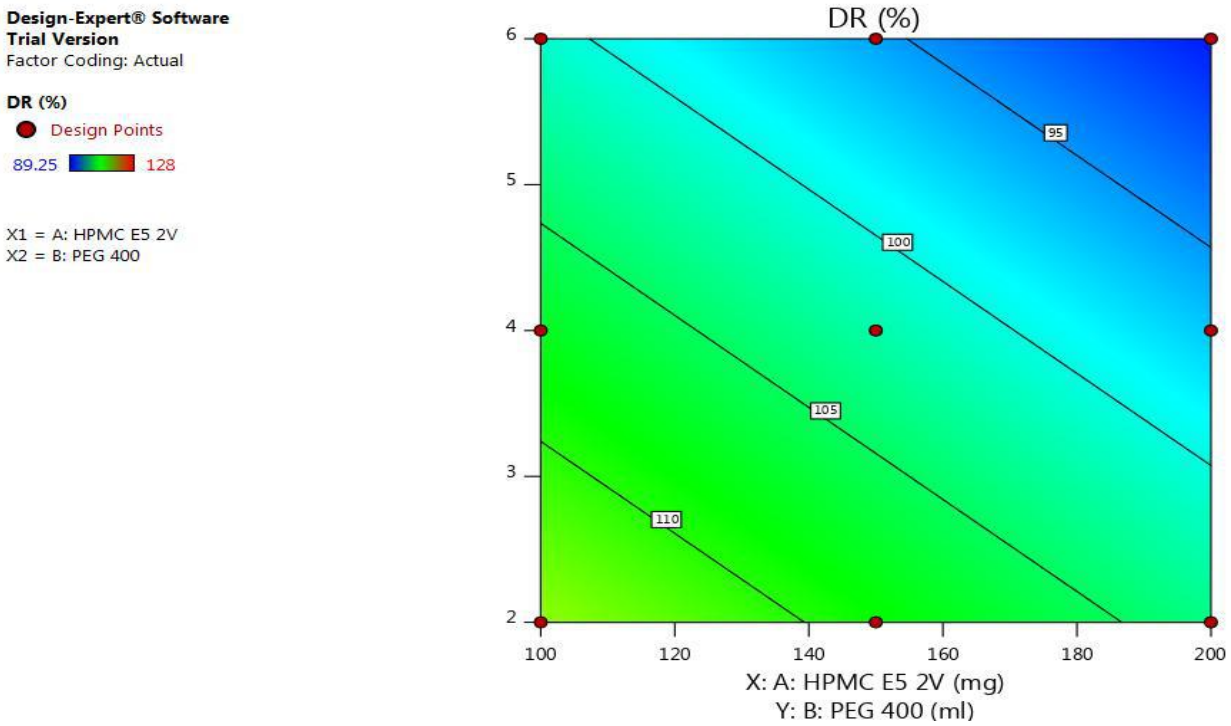

Fig 5.17: Contour plots showing the effect of amount of HPMC(X_1) and PEG 400(X_2) on response drug release.

Evaluation parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)	0.19± 0.09	0.20±0 .02	0.17±0.0 1	0.22±0.0 4	0.31±0.04	0.28±0. 01	0.33±0.0 3	0.21±0.0 2	0.23±0. 05

Weight variation (mg)	33.31 ±2.54	25.61± 11.21	51.31±3. 94	32.37±2. 10	31.5±1.91	42.8±3. 05	32.8±2.0 2	32.42±2. 11	42.2±3. 50
Surface pH	7.0	7.0	6.89	6.90	7.0	6.69	6.90	6.70	7.0
Folding endurance	110±2	99±1	92±3	93±2	101±4	113±2	96±5	94±3	94±2
Uniformity of drug content	99.62	98.28	99.11	98.30	99.2	98.7	97.08	98.66	97.96
Tensile strength (kg/mm^2)	3.29	3.86	4.13	3.09	3.95	4.08	2.25	3.99	4.9
In-vitro disintegration time (sec)	21±2	24.2±2	22±4	21±2	23±3	22±4	20±3	25.6±2	25.3±2

***All values shown here are Mean±S.D n=3**

Table 5.9: Results of desired evaluation parameters of optimization batches (F1-F9) of Vardenafil oral fast dissolving film

Weight variation

The mean weight variation were found in the range of 20-50 mg within the respective group of F1-F9 weight variation was uniform.

Uniformity of thickness:

Thickness was measured using Vernier Calipers. Thickness of all the films was in the range of 0.19±0.23 mm indicating that there was not much difference in the thickness within the formulations and was within the limit. As the concentration of polymer increases thickness gradually increases. It is essential to ascertain uniformity of film thickness as this is directly related to accuracy of dose distribution in the film

Folding Endurance

It was observed that, with increase in the polymer concentration, there is an increase in folding endurance. The folding endurance values ranges from to 92 to 110 times. The result indicates that all the formulations had ideal film properties.

Surface pH

The surface pH of the strips was ranging from 6.to7.0 The almost neutral values of surface pH of films assured that there will be no irritation to the oral mucosal lining and easily acceptable by patients

Tensile strength

The tensile strength was ranging from 2.25±4.09 kg/ mm2 showing an increase in tensile strength with increase in the concentration of polymer. The tensile strength gives an indication of film strength which is important to resist the mechanical movements that may occur during the Packing, Storage and Shipping of the films.

Drug Content Uniformity

Content uniformity test was performed to ensure uniform and accurate distribution of drug. The % drug content of Various Formulations ranged from 83.49±0.540 to 98.46±0.515 %. The drug content data revealed that there was no significant difference in the uniformity of the drug content.

Disintegration Time

In-vitro disintegration study of Vardenafil Oral Fast Dissolving film in phosphate buffer pH 6.8 at specific time interval .The mean time for complete Disintegration of oral film was obtained below 25 s indicating that as the concentration of plasticizer increased, Disintegration of film was also increased.

IN-VITRO DRUG RELEASE STUDIES

S.no	Time (min)	F1	F2	F3
1	0	0	0	0
2	1	24.025	15.41	19.282
3	2	46.614	32.94	38.358
4	3	64.626	48.69	56.564
5	4	85.779	67.95	79.474
6	5	96.35	89.25	94.999

Table 5.10: In-Vitro Drug Release Studies of F1, F2&F3

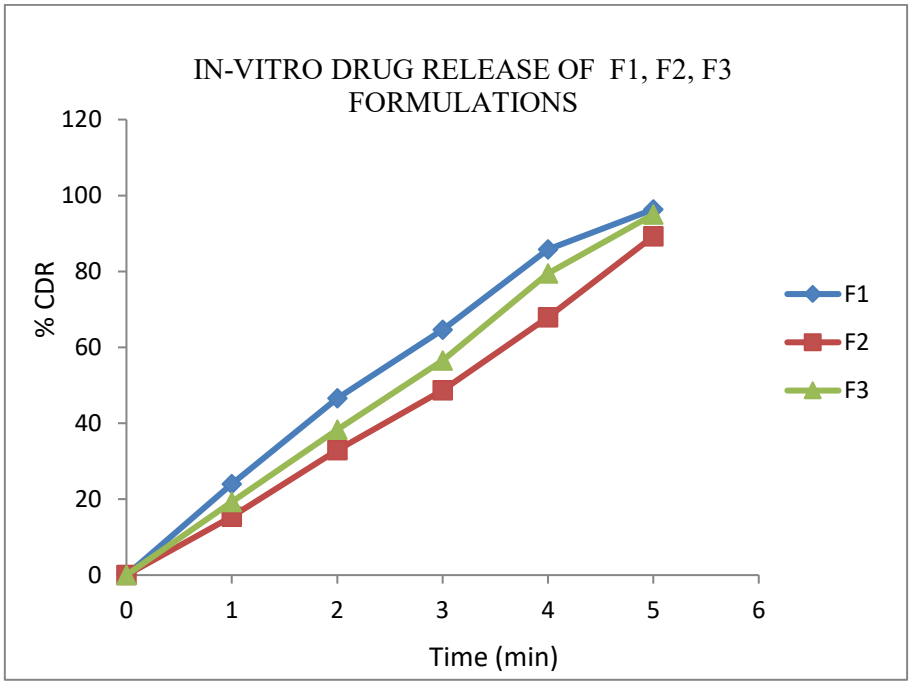

Fig 5.18: Drug Release Graph of F1, F2&F3

S.no	Time (min)	F4	F5	F6
1	0	0	0	0
2	1	15.525	10.641	20.4743
3	2	29.153	25.333	35.1794
4	3	46.947	39.256	53.0768
5	4	62.754	52.397	71.051
6	5	78.638	74.7816	89.2561

Table 5.11: In-Vitro Drug Release Studies of F4, F5&F6

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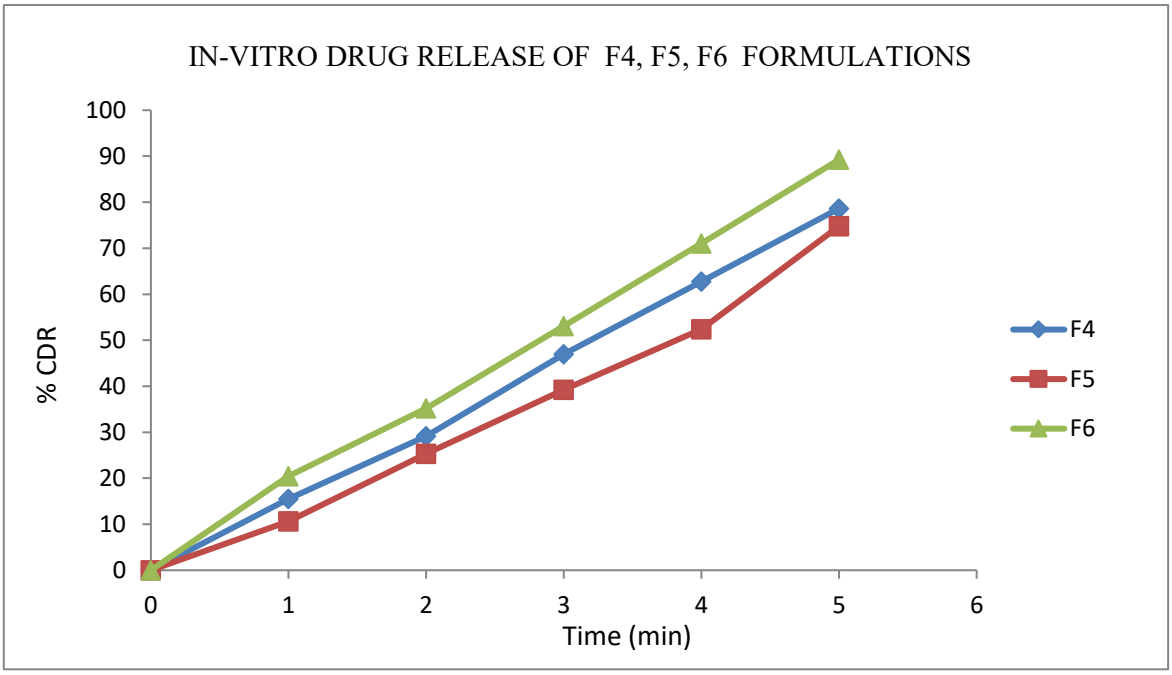

Fig 5.19: In-Vitro Drug Release Graph of F4, F5 & F6

S.no	Time (min)	F7	F8	F9
1	0	0	0	0
2	1	15.0897	18.141	22.7051
3	2	33.2503	36.141	38.2051
4	3	50.4614	54.1666	56.9486
5	4	69.7049	75.356	78.7434
6	5	87.5741	89.586	92.6023

Table no 5.12: In-Vitro Drug Release studies of F7, F8&F9

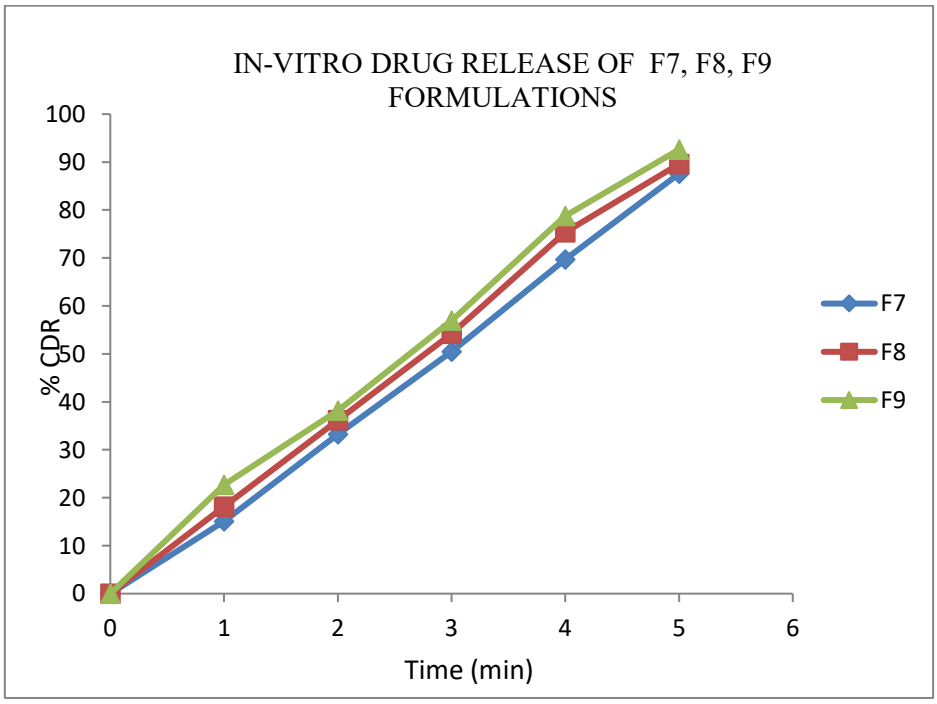

Fig 5.20: In-Vitro Drug Release Graph of F7, F8&F9

In vitro drug release was found to decrease with increase in the film forming polymer concentration which may be due to increase in the thickness of the oral strip and due to increase in the time required for wetting and dissolving the drug molecule present in the polymeric matrix but increase with increase in the concentration of the polymer. Formulations F1, F2, and F3 showed drug release up to 96.35%, 89.25%, and 94.999%, respectively, as shown in Figures 5.16,5.17,5.18.Formulations F4 ,F5 ,F6 showed drug release up to 78.63, 74.78, 89.25%,Formulations F7,F8,F9 showed drug release up to 87.9%,89.2%,99.6% at an interval of 5 min. Film formed with higher quantity of polymer had shown slower dissolution rate; this might be due to the increase level of HPMC that results in formation of high viscosity gel layer due to more intimate contact between the particles of polymer resulting in decrease in the mobility of drug particles from the swollen matrix, which leads to a decrease in the release rate .

The formulation F1 showed a maximum percentage drug release of 96.6% in 5 min as shown in figure 5.16. in medium 6.8 phosphate buffer .reflection at 5 min might be due to complete solubilization of drug and faster dissolution rate. Percentage release in 5 min at pH 6.8 of saliva is an essential parameter and hence it was selected as response of design. It was observed that all batches showed Q_5min more than 85% but batches showed lowest Q_{5min} compared to that of other batches. Batch F1 Formulation showed more drug release as compared to other so F1 is considered to be the best and optimized formulation.

EX-VIVO PERMEATION STUDY

Ex-vivo permeation Drug release of Optimized Formulation.(F1)

Time (in min)	% cumulative drug release
5 min	21.833
10 min	143.974
15 min	67.4611
20 min	91.640
25 min	118.409
30 min	145.678

Table 5.13: Ex-vivo permeation release of optimized formulation (F1).

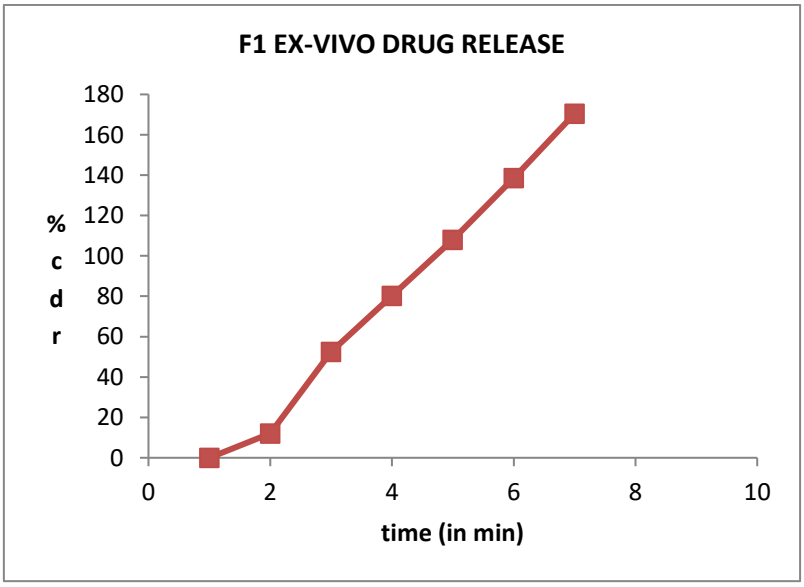

Fig 5.21: Ex-vivo permeation drug release of optimized formulation(F1)

The permeation studies were carried out in a Franz diffusion cell by placing the film (size 1 × 1 cm^2) over the porcine cheek pouch. The drug transported across the membrane was measured periodically. A plot of cumulative amount of

drug permeated against time (for a period of 30 min) exhibited a typical permeation profile substantiating the potential of Buccal delivery of Vardenafil. It was observed that the permeation rate of Vardenafil was relatively constant throughout the study period. The amount of drug transported across the buccal membrane progresses with increase in duration and the cumulative amount at various time periods was found to be143.974 at 10 min, Furthermore, the cumulative amount of Vardenafil Permeated at the end of the study period (30min) was 145.67%. The data observed in this study substantiate the potential of the prepared film to deliver a significant amount of Vardenafil through the buccal mucosa.

6. CONCLUSION

The quality of film was affected by type and concentration of polymer and plasticizer. The development of oral film drug delivery of Vardenafil is one of the alternative routes to provide immediate action. In addition, this formulation enhances patient compliance, especially for outpatient setting. The results of present study indicated that HPMC E52V could be used as a film forming polymer for formulation of fast dissolving film and PEG 400 as a plasticizer and sucrose as sweetener was formulated at lab –scale Based on results of pre-liminary trials it can be concluded that PEG 400 as plasticizer ,and sucrose as sweetener are compatible ,inert and effective to maintain overall quality and flexibility of resulting film . On the basis of data obtained from *in vitro* dissolution studies it was concluded that F1 is promising formulation suitable for the immediate release of Vardenafil..A3^2 factorial design was applied considering that HPMCE52V and PEG 400 as Independent variables and Tensile strength, disintegration time, drug release are taken as Dependent variables. Batch F1 formulation showed was considered to be optimized and showed more drug release and less disintegration time. Hence it can be summarized that HPMC and PEG 400 are comapatable, inert smooth mouth feel to formulate oral films. Fast dissolving film can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

Oral fast dissolving film of Vardenafil was successfully formulated at lab-scale by solvent casting method.HPMC$E_5 2_V$ is used as polymer and PEG 400 is used as plasticizer, sucrose as sweetening agent and citric acid as saliva stimulating agent. The films are compatible, inert, and effective to maintain overall quality, flexibility of resulting oral fast dissolving film. They were evaluated successfully for the characterization studies like FT-IR,DSC,SEM.A 3^2 factorial design was applied and independent variables were taken as (X_1) amount of HPMC $E_5 2_v$ and (X_2) amount of PEG 400,and dependent variables were taken as (Y_1) disintegration time(Y_2) tensile strength, Drug release % (Y_3).among all the formulations F1-F9 Optimized formulation F1 showed good results in drug release with 96% and excellent mechanical properties of oral fast dissolving film, easy peeling of film from surface of glass, excellent palatability, very smooth mouth feel ,easy in handling. Hence,it can be concluded that Vardenafil was successfully prepared by solvent casting method using PEG 400 as best compatible plasticizer, and sucrose as sweetener respectively Optimized formulation F1 ,exhibited good results, with excellent mechanical properties and easy peeling off.

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