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# Design and evaluation of sildenafil citrate fast dissolving film for treatment of erectile dysfunction

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**ABSTRACT**

*Sildenafil citrate is one of the most effective agents for treatment of erectile dysfunction which acts by inhibiting the cGMP-specific phosphodiesterase type 5. Extensive research work is focused on flash release dosage forms and especially fast dissolving films are successful to attract pharma-industry due to ease of preparation and opportunity to extend patent life. Films are widely acceptable in patients too because of quick onset and user friendliness. The aim of present study was to prepare fast dissolving films of sildenafil citrate which provides product differentiation from other marketed products and also quick disintegration of highly bitter drug with satisfactory taste masking in oral cavity. Film formulation can be taken within the pocket and patient can take it without need of water by simply putting it on tongue without any grittiness that is frequently found during disintegration of orodispersible tablets. The developed formulation will disintegrate within minute and ultimately provides good bioavailability and quick onset. The DSC studies showed that drug had no interaction with polymer or other additives. The IR studies confirmed complete complexation of drug with taste masking resin. Using experimental design, the prepared formulations were evaluated for in vitro dissolution, solution time and their physicomechanical parameters mainly tensile strength. The optimized formulation (batch OT6) containing HPMC E15, propylene glycol, glycerin and Kyron T-134 showed drug dissolution (more than 90% within 10 min) with satisfactory taste masking and other physicomechanical properties that were suitable for mouth dissolving film.*

**Keywords**: Fast dissolving oral film, Sildenafil citrate, Solvent casting, Quality by design, Taste masking.

## INTRODUCTION

Erectile dysfunction is defined as per consensus statement of impotence 1993 by national institute of health as the persistent inability to achieve and /or persist an erection required for satisfactory sexual performance [1]. According to epidemiological surveys, one in five men experiences impaired erection in population. As per a population based survey, Erectile dysfunction is commonly reported in 30% elder than 69 years, 22% patient between 60 to 69 years and 12% patients younger than 59 years [2] . cGMP-specific phosphodiesterase type 5 (PDE5), enzyme responsible for degradation of cGMP, is inhibited by sildenfil citrate. The inhibition of phosphodiesterase type 5 (PDE5) by these drug increases the amount of cGMP which causes relaxation of smooth muscle and ultimately increases blood flow into the corpus cavernosum. Sildenafil citrate has been successfully proved effective to cure erectile dysfunction. Patients may take sildenafil citrate from 0.5 h to 4 h before starting sexual activity [3]. Sildenafil citrate is highly bitter BCS Class I drug and taste masking of highly bitter drug is challenging when dosage form is designed to disintegrate in oral cavity. Generally water soluble low dose actives are considered ideal candidate for fast dissolving films. Dose of sildenafil is high (35.11 mg sildenafil citrate equivalent to 25 mg sildenafil) and loading of high dose bitter active with satisfactory taste masking in small film is itself a big challenge for formulation scientist without affecting its physical and chemical attributes. Satisfactory complexation with acceptable content uniformity is itself a big challenge when drug-resin complex is in suspended form [4].

Oral drug administration is most preferred route of administration due to the aspect of patient compliance. Fast dissolving film is ultrathin strip, which has similar shape and size to postage stamp, with actives and mostly water soluble excipients mainly film forming polymers and plasticizers. The fast dissolving films have larger surface area compared to orodispersible tablets (ODTs) that leads to rapid disintegration in mouth. Unlike the orodispersible tablets which are brittle and fragile in handling, films are flexible enough with adequate ease of transport and handling. Like the other liquid dosage forms, precise dosing and unit dose formulation is possible with fast dissolving films. Films provide ease of swallowing and patient can take it without need of water [5-6].

The aim of the present research was to develop fast dissolving film of sildenafil citrate which not only provides rapid onset but also provides unique product differentiation from other marketed product such as film coated tablets, effervescent tablets, chewable tablets etc. A $3^2$ full factorial design was used for optimization and selection of final formulation. Present investigation will provide the formulation which can be taken within the pocket and patient can take it without need of water by simply putting it on tongue. The patient will not feel any discomfort and grittiness during and/or immediately after dissolution, frequently found during disintegration of orodispersible tablets. The developed formulation will disintegrates in fraction of minute with satisfactory taste masking and quick release compared to widely consumed film coated tablets. Present investigation will provide formulation which is formulated by simple continuous process (mixing, casting, drying & cutting) compared to film coated tablets involving many unit operations.

## EXPERIMENTAL SECTION

### Materials

Sildenafil citrate (Rakshit Drugs Pvt. Ltd, Andhrapradesh, India), Methocel™ (HPMC) E6; Methocel ™ (HPMC) E15 (Colorcon Asia Pvt. Ltd, Goa, India), Kyron™ T-134; Kyron™ T-114 (Corel Pharma Chem., Ahmedabad, India), Indion® 254 ; Indion® 234; Indion® 204 (Ion Exchange India Ltd., Mumbai) were received as gift samples. Ponceu 4R (Roha Dye Chem., Mumbai, India), Pipermint Flavor-solid (SK Flavors and fragrances, Ahmedabad, India), Sucralose (JK sucralose Inc., India), Menthol (Shreeji chemicals, Ahmedabad), Polyethylene glycol (PEG 300), Glycerin; Propylene glycol (Finar Chemicals Ltd, Ahmedabad, India) were procured. All other materials and excipients used were of either pharmaceutical or analytical grade.

### Drug excipient compatibility study

Possible interaction of drug with various excipients proposed for use in final formulation was checked by using differential scanning calorimetry (DSC). DSC study of pure drug, excipients and their combination used in final optimized formulation OT6 was carried out using DSC instrument (DSC-60, Shimadzu, Kyoto, Japan) at Shri S. K. Patel College of Pharmaceutical Education and Research, Kherva, Ganpat University. In this process, samples (3-5 mg) were put into aluminium cell and scanned at 50- 300 °C, at 10°C per minute rate under nitrogen atmosphere against blank DSC aluminium cell as a reference.

### Analytical method development

Calibration curves of sildenafil citrate were taken in deionized water. Accurately weighed 100mg of sildenafil citrate was transferred to 1000 mL volumetric flask and dissolved in deionized water respectively. The volume was adjusted up to 1000 mL with deionized water to get 100 µg /mL stock solution of drug. The stock solution (100 µg/mL) was further diluted to get concentration of sildenafil citrate in the range of 10-35 µg/mL for respective buffer. These solutions were scanned for the maximum absorbance using Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). The absorbance of all drug solutions was estimated at λmax.

### Formulation strategy as per Quality by design elements

Before designing the experimental work, Quality target product profile (QTPP) and Critical quality attributes (CQA) of product are necessary to identify for better understanding of our target formulation. QTPP is a prospective summary of the quality characteristics of a product that will be achieved to ensure the desired safety, quality and efficacy of the drug product ideally. CQA is a chemical, physical, biological or microbiological property that should be within an appropriate range to ensure the desired product quality [7-9].

### Screening study for drug resin complex

Selection of resin is dependent on cationic and anionic nature of the drug and requirement of formulation. Since sildenafil citrate is anionic molecule [10], weak cation exchange resins such as Indion 204, Indion 234, Indion 254, Kyron T-134 and Kyron T-114, were selected for the study. For preliminary screening study, drug: resin was taken in 1:1 ratio. An accurately weighed quantity of resin (1 g) was taken in a 100 ml glass beaker containing 25 ml of deionized water. Resin was allowed to swell for 30 min. 1g drug was added into the same beaker and pH of solution was recorded. The beaker was placed on a magnetic stirrer for 30 min at 30°C. The solution was filtered with

whatman filter paper and filtrate was analyzed using appropriate dilution in the range of 10-35 µg/mL for determination of unbound drug at 294 nm using Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). The residue on filter paper was dried at 40° in a hot air oven. Percentage of drug bound to resin was calculated from amount of unbound drug. This procedure was performed for all resins separately.

**Optimization trials for evaluation of drug-resin complexation process**

The optimization of drug- resin complexation process of Kyron T-134 and Indion 234 was performed by determining the effect of various factors on complexation. One factor at one time approach was adopted for optimization [11].

(a) Effect of soaking time of resin on complexation

Accurately weighed quantity of selected resin (1g) was soaked in 25 ml of deionized water for 5, 10, 15, 20, 30 and 45 min. Accurately weighed quantity of sildenafil citrate (1g) was added to previously soaked resins. The solutions were stirred for 30 min at 30°C. The mixture was filtered and the filtrate was analyzed for bound drug.

(b) Effect of stirring time on complexation

Accurately weighed quantity of selected resin (1g) was soaked in 25 ml of deionized water for 30 min. Accurately weighed quantity of sildenafil citrate (1g) was added to previously soaked resins. The solutions were stirred for 30, 60, 90, 120 and 150 min at 30°C and analyzed for bound drug.

(c) Effect of temperature on complexation

Accurately weighed quantity of selected resin (1g) was soaked in 25 ml of deionized water for 30 min. Accurately weighed quantity of sildenafil citrate (1g) was added to previously soaked resins. The solutions were stirred for 120 min at 10, 20, 30, 40 and 50°C and analyzed for bound drug.

(d) Effect of pH on complexation

Accurately weighed quantity of selected resin (1g) was soaked in 25 ml of solution of pH 1.2, 2, 3, 4, 5, 6, 7 and 8 (prepared from standard solutions of 0.1N hydrochloric acid and 0.1N sodium hydroxide solutions) for 30 min. Accurately weighed quantity of sildenafil citrate (1g) was added to previously soaked resins. The solutions were stirred for 120 min at 30°C and analyzed for bound drug.

(e) Effect of drug: resin ratio on drug-resin complextion

Accurately weighed quantity of drug (1g) was taken and added to the resins as per drug: resin ratio of 1:0.25, 1:0.5, 1:0.75, 1:1, 1.1.25 and 1:1.5. The resins were previously soaked in 25 ml of deionized water for 30 min. The solutions were stirred for 120 min at 30°C and analyzed for bound drug.

**Characterization and evaluation of drug resin complex by IR spectroscopy**

Pure drug, pure resin and drug resin complexes were subjected to fourier transform infrared spectroscopy (FTIR) studies by FTIR-1700 instrument, Shimadzu, Kyoto, Japan at central instrument laboratory of the Shri Sarvajanik Pharmacy College, Mehsana using KBr mixing method. Apart from pure drug and pure resin, drug- resin complexes of 1:0.75 were evaluated by IR spectroscopy. The spectrum of drug-resin complex was compared with spectra of pure drug and pure resin, to confirm drug resin complex formation.

**Preparation of fast dissolving films containing sildeanfil citrate**

For BCS class I bitter tasting drugs like sildenafil citrate, taste masking is a critical factor for patient acceptance aspect. Effect of different drug resin (Table 7) suggested that satisfactory complexation of drug: Kyron T-134 was achieved at ratio 1:0.75 and 1:1. Films were formulated by solvent casting method. Methocel, propylene glycol, glycerin, menthol, ponceu 4R, pippermint flavor and sucralose were selected as film former, plasticizer, humectant, cooling agent, coloring agent, flavor and sweetening agent respectively. Compositions of sildenafil loaded films were shown in Table 1. Briefly Kyron T-134 was soaked in purified water for 30 min at room temperature and then sildenafil citrate was added under continuous stirring and stirred for 120 min to make complexation. Menthol was dissolved in propylene glycol in separate glass beaker and then this solution was added to drug-resin complex. Polymer, color, sweetener, flavor and humectants were added subsequently to beaker containing drug-resin complex under continuous gentle stirring. After complete removal of bubbles, 3.014 g dispersion was casted on glass petriplate with surface area of 50.24 cm2 (Diameter: 8cm). The glass petriplate was kept in controlled temperature oven (Vinayak Pharma Technology, vatva, India) at 50°C for 5 hr. After drying, films were peeled and cut into dimension of 10.5 $cm^2$ (3.5 cm X 3 cm) and store in triple laminated alu pouch. These films were further subjected to various evaluation tests.

**Table 1. Preparation of fast dissolving film containing sildenafil citrate**

| Components | Preparation of fast dissolving film containing sildenafil citrate<br>Formula ( mg/ unit film of 10.5 $cm^2$) | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| Sildenafil citrate | 35.57 | 35.57 | 35.57 | 35.57 | 35.57 | 35.57 | 35.57 |
| Kyron T-134 | 35.57 | 35.57 | 26.67 | 26.67 | 26.67 | 26.67 | 26.67 |
| HPMC E6 | 74 | 74 | 74 | 74 | - | - | - |
| HPMC E15 | - | - | | - | 60 | 55 | 55 |
| Propylene glycol | 19 | 25 | 19 | 25 | 25 | 25 | 25 |
| Glycerin | - | - | - | - | - | - | 10 |
| Sucralose | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Menthol | - | - | - | - | - | - | 1.5 |
| Ponceu 4R | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Pippermint flavor | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Purified water* | | | | Q.S. | | | |
| Evaluation parameters | | | | | | | |
| Tensile strength ( kg/cm2) | 0.062± 0.005 | 0.065± 0.006 | 0.083± 0.005 | 0.085± 0.006 | 0.370± 0.006 | 0.317± 0.004 | 0.330± 0.001 |
| Disintegration time@(Sec.) | 11.24± 0.12 | 13.26± 0.17 | 16.38± 0.07 | 16.51± 0.12 | 51.57± 0.21 | 40.41± 0.12 | 40.11± 0.08 |
| Solution time@ (Sec.) | 1.42 ± 0.27 | 2.01 ± 0.09 | 2.19 ± 0.08 | 2.24± 0.11 | 5.01± 0.08 | 4.17± 0.17 | 4.12± 0.12 |
| Folding endurance | 17±2 | 20±3 | 27± 3 | 29± 3 | 132± 7 | 107± 4 | 111± 4 |
| Surface pH | 6.45 ± 0.08 | 6.47± 0.09 | 6.35± 0.02 | 6.32 ±0.01 | 6.57± 0.12 | 6.52± 0.12 | 6.47± 0.02 |
| Thickness (mm) | 0.18 ± 0.02 | 0.22 ± 0.01 | 0.14± 0.02 | 0.14 ± 0.02 | 0.23± 0.02 | 0.22± 0.02 | 0.22± 0.02 |
| Appearance & Surface texture | Light pink colored opaque film with rough surface | | | | | | |
| *@ Disintegration time and solution time varies in range of ±4 Sec* | | | | | | | |
| ** Up to 630 mg per unit film.3.014 g solution was casted per each petriplate with surface area of 50.24 cm2 ( Diameter 8cm)* | | | | | | | |

## Optimization of sildenafil film formulation using $3^2$ full factorial designs

From the results of screening study, the optimization was carried out using design of expert (DOE) approach. To study the effect of two independent variables on three different quantitative levels i.e. concentration of HPMC E15 ($X_1$) and concentration of propylene glycol (X2) on responses, $3^2$ full factorial design was used. In this design, concentration of HPMC E15 and propylene glycol were used as independent variables while tensile strength, disintegration time and % drug release at 10 min were selected as response variables. The detailed layout of factorial batches is shown in Table 2. The equations containing independent variables and response terms were obtained by subjecting the results to statistical evaluation. Design Expert 9.0.4.1 (Built date February 23, 2015) was used to calculate multiple linear regressions to determine the control factors that mainly affect the responses.

Polynomial equation for $3^2$ full factorial design: $Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2$ was used. In this equation, Y is the dependent variable, $b_0$ is the arithmetic mean response of the factorial trial runs, and bi is the estimated coefficient for the factor Xi. The significant factors in polynomial equations were selected by stepwise forward and backward elimination for regression analysis. The terms of full model having non-significant p value ($p > 0.05$), which have negligible contribution, were neglected.

**Table 2. Detailed layouts of Optimization trials using $3^2$ full factorial design**

| Ingredients | Formula ( mg/ unit film of 10.5 $cm^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | OT1 | OT2 | OT3 | OT4 | OT5 | OT6 | OT7 | OT8 | OT9 |
| Sildenafil citrate | 35.57 | 35.57 | 35.57 | 35.57 | 35.57 | 35.57 | 35.57 | 35.57 | 35.57 |
| Kyron T-134 | 26.67 | 26.67 | 26.67 | 26.67 | 26.67 | 26.67 | 26.67 | 26.67 | 26.67 |
| HPMC 15cps | 40 | 40 | 40 | 45 | 45 | 45 | 50 | 50 | 50 |
| Propylene glycol | 20 | 25 | 30 | 20 | 25 | 30 | 20 | 25 | 30 |
| Glycerin | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Sucralose | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Ponceu 4R | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Menthol | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Pippermint flavor | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Purified water | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| Independent variable | Coded Value | | | | Actual Value (mg) | | | | |
| HPMC 15 CPS | -1 | 0 | | +1 | 40 | 45 | | 50 | |
| Propylene glycol | -1 | 0 | | +1 | 20 | 25 | | 30 | |
| ** Up to 630 mg per unit film.3.014 g solution was casted per each petriplate with surface area of 50.24 cm2 ( Diameter 8cm)* | | | | | | | | | |

**Evaluation of fast dissolving film of sildenafil citrate**

The prepared films were evaluated for tensile strength, surface pH, folding endurance, thickness, *in vitro* disintegration, solution time, assay and *in vitro* dissolution studies. The tensile strength of the film was evaluated by using the push pull tensiometer instrument. It consists of two load cell grip in which the upper one was movable and the lower one was fixed. Films with dimensions of 3.5×3 $cm^2$ were fixed between both cell grips and force was applied gradually till the film break. The break force was taken directly from the dial reading in g. It is calculated by equation, tensile strength = break force/area of film in $cm^2$ [12, 13]. Folding endurance of the film was measured by folding the film at the same point until it breaks. The number of folds before the film breaks is the folding endurance of the film. The surface pH of film was checked to study irritability of film in vivo. Extreme acidic or alkaline pH may cause irritation to oral mucosa, it was decided to keep the surface pH as near to neutral pH as possible. Film was dissolved in 20 ml deionized water. The pH was measured by dipping the combined pH electrode in this solution [14]. A thickness of the film was measured by using micrometer screw gauge. Film was measured at three positions i.e. central and the two corners and the mean thickness was calculated [12]. The *in vitro* disintegration time is the time at which the film starts to break. The disintegration time was measured in a beaker containing 20 mL deionized water. The time at which film starts to break was measured as disintegration time of film. The time at which the film completely dissolves is considered as dissolution time or solution time [15, 16]. The assay was done by dissolving one film of dimension 3.5 cm × 3 cm containing 25 mg of sildenafil citrate in 0.01N hydrochloric acid in 100 mL volumetric flask under continuous shaking for about 20 min. If any large undispersed fragments of film were seen, sonication was performed for 5 min to disperse film fragments residues. The above solution was further diluted to get concentration of sildenafil citrate in range of 10-35 µg/mL. The experiments were carried out thrice for all formulations and average was recorded. The *in vitro* dissolution study of sildenafil fast dissolving film was performed using USP apparatus II - paddle (model TDT-08T, Electrolab, Mumbai, India) fitted (100 rpm) maintained at 37 ± 0.5$^oC$. Dissolution media was 900 mL of 0.01N hydrochloric acid and tested for drug release up to 20 min. During the study, 10 mL of aliquots were withdrawn at 5, 10, 15 and 20 min and were replaced by fresh 0.01N hydrochloric acid. Collected aliquots were filtered through a 0.45$\mu$m membrane filter, diluted and assayed using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan) at 294 nm. Cumulative percentage drug release was calculated using calibration curve equation of drug.

**Taste evaluation study by spitting**

8 healthy adult male volunteers with age limit of 24–42 years participated in a single dose, two treatment and single blind study. Before the study, written informed consent was taken from all volunteers and they were informed about purpose, risk and duration of the study. Optimized test formulation and reference formulation (formulation without taste masking resin) were given to each volunteer randomly. Before the study, the volunteers were asked to rinse their mouth with 200 mL of distilled water. The volunteers were requested to put film in mouth for 3 min, record the disintegration time of the film sample and give the score based on the parameters, namely mouth feel, taste or bitterness, after taste of film, ease of handling and overall acceptance of formulation as given in Table 3. The volunteers were asked to spit out the sample with saliva after 3 min and asked to rinse their mouths with 200 mL of distilled water. The same procedure was repeated after 2 hr for second sample (either test or reference sample). Drug was complexed with resin which can be dissociated in stomach, not in saliva. So, spitting of formulation and saliva was instructed to volunteers to prevent exposure of drug [17-19].

**Table 3. Parameters, score and results of taste evaluation study**

| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Mouth feel | Gritty /Irritating | Gritty | Slightly Gritty | Smooth | Very smooth |
| Taste ( Bitterness) | Very bitter | Bitter | Slightly bitter | Slightly sweet/ Acceptable | Very sweet |
| After taste | Very Bitter | Bitter | Slightly bitter | Slightly sweet/ Acceptable | Very sweet |
| Ease of handling | Very brittle | brittle | Acceptable and does not break | Flexible and easy to handle | Patient friendly and very easy to handle |
| Acceptance | Very poor | Poor | Acceptable | Good | Excellent |

| Results of taste and palatability evaluation | | | | | | |
|---|---|---|---|---|---|---|
| | Mouth feel | Taste (Bitterness) | After taste | Ease of handling | Acceptance | *In vivo* disintegration time |
| Test (Batch No. OT6) | 4.25 ±0.46 | 4.00 ±0.00 | 3.88 ±0.35 | 5.00 ±0.00 | 4.375 ±0.52 | 27.75±7.52 ( Min:20 sec, Max:41 Sec) |
| Reference (Film without Resin) | 4.13 ±0.35 | 1.75 ±0.46 | 1.13 ±0.35 | 5.00 ±0.00 | 1.75 ±0.46 | 19.00±2.93 ( Min:15 sec, Max:24 Sec) |

**Stability Study of Optimized Formulation**

Stability study of batch OT6 was conducted at accelerated condition (40ºC ± 2ºC and 75 ± 5% RH) in the stability chamber for 3 months and 6 months. Films were packed in triple laminated alu pouches. All evaluation parameters and dissolution test were performed at 3 months and 6 months.

## RESULTS AND DISCUSSION

**Drug- excipients compatibility study**

DSC thermogram of Sildenafil citrate (Fig. 1) revealed a sharp endothermic peak at 200.28°C. DSC thermogram of excipient mixture (Fig. 2) showed characteristic endotherms at 89.23°C. In drug–excipient mixture (Fig. 3), sharp endotherm of sildenafil citrate was very slightly shifted to 187.66°C with retained characteristic peak of excipient at 89.23° which showed absence of any physical compatibility of drug with excipients used in final formulation.

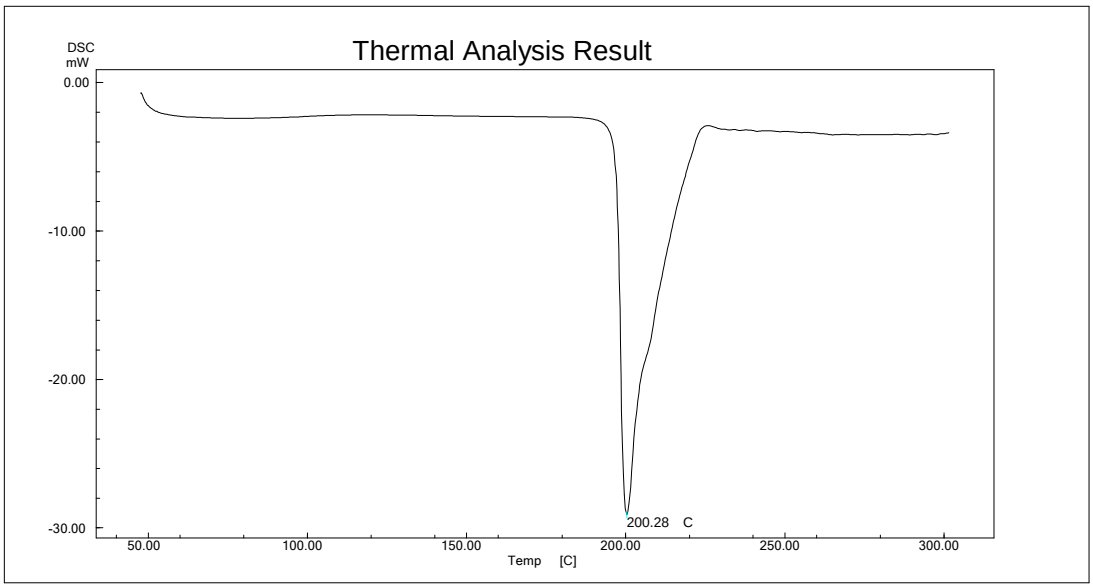


**Figure 1. DSC thermogram of sildenafil citrate**

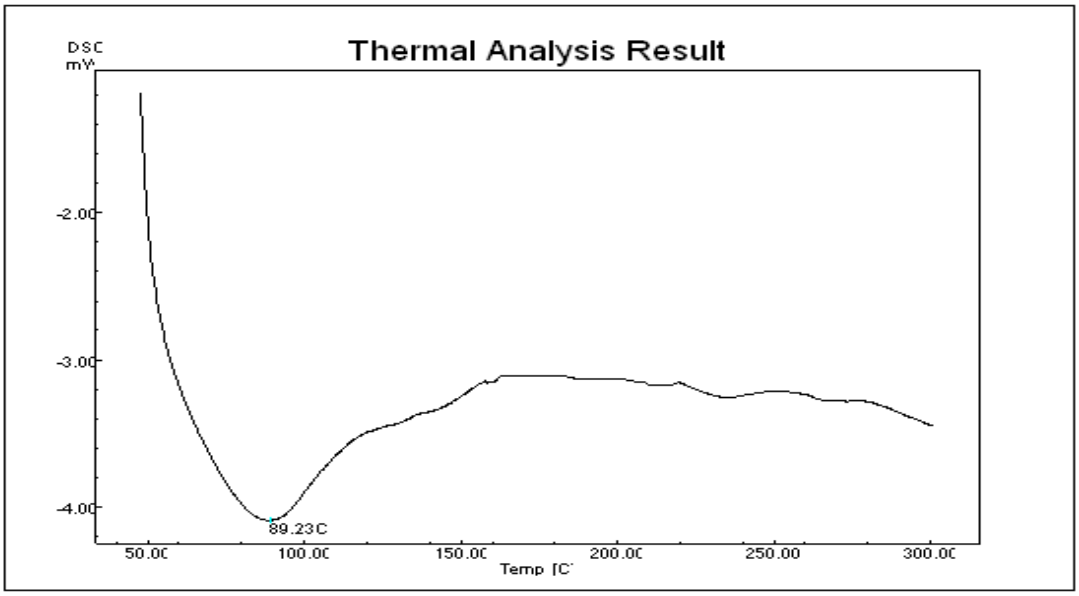


**Figure 2. DSC thermogram of excipient combination**

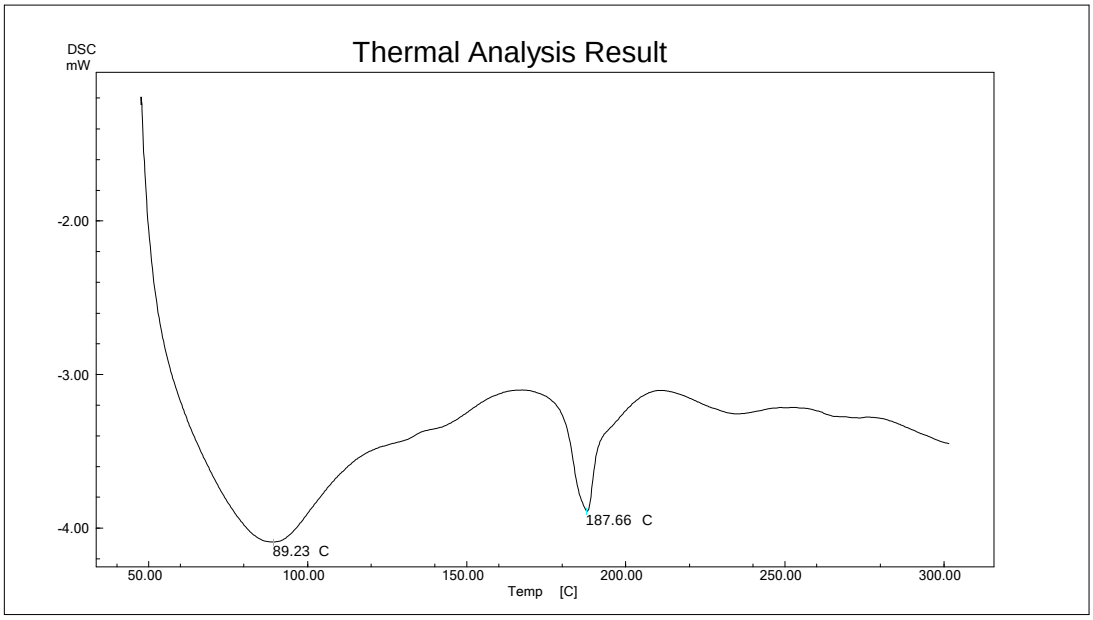


**Figure 3. DSC thermogram of sildenafil and excipients mixture**

## Analytical method development

The drug exhibited λmax at 294 nm. The calibration curve was generated using different concentration (10-35 µg/mL) of drug solutions in the Beer-Lambert law. The data of calibration curve is shown in Table 4 and calibration curve is shown in Fig. 4.

**Table 4. Calibration curve data of drug in demineralized water**

| Concentration (µg/ml) | Absorbance | | | Average Absorbance ± SD (n=3) |
|---|---|---|---|---|
| | I | II | III | |
| 10 | 0.204 | 0.208 | 0.212 | 0.208±0.004 |
| 15 | 0.311 | 0.311 | 0.311 | 0.311±0.000 |
| 20 | 0.419 | 0.411 | 0.415 | 0.415±0.004 |
| 25 | 0.520 | 0.521 | 0.519 | 0.519±0.001 |
| 30 | 0.620 | 0.620 | 0.620 | 0.620±0.000 |
| 35 | 0.733 | 0.734 | 0.735 | 0.734±0.001 |

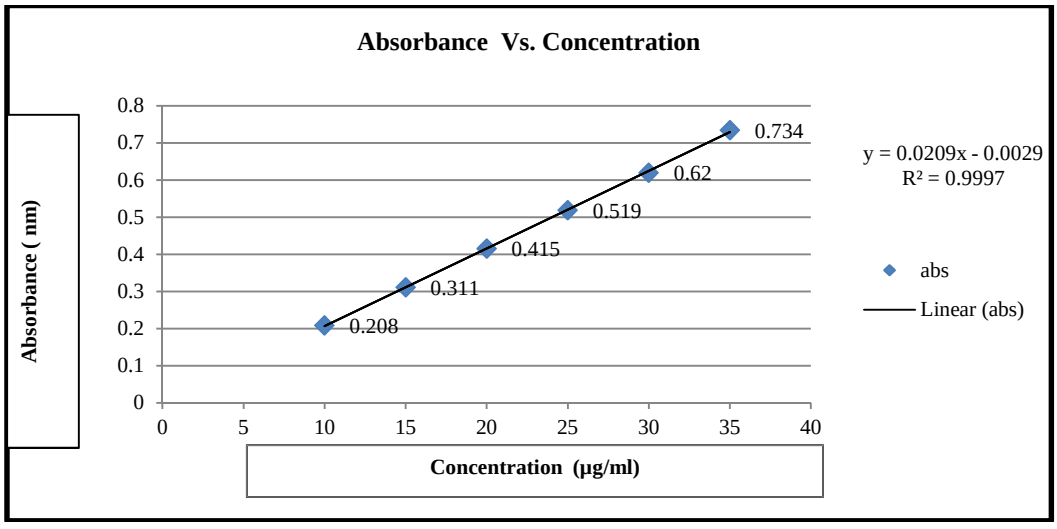


**Figure 4. Calibration curve of sildenafil citrate in demineralized water**

**Formulation strategy as per Quality by design elements**

Predetermined QTPP of formulation was oral, fast dissolving, single layer, 3.5 cm X 3 cm sized rectangular film containing sildenafil citrate eq. to 25 mg sildenafil which may be taken half an hour before starting sexual activity with satisfactory stability profile in Aluminium- PET (Polyethylene) laminated pouches. Taste, disintegration time, content uniformity and dissolution were considered as CQA of formulation because safety, patient compliance and efficacy will directly be linked to these factors.

**Screening study for drug resin complexation**

Results of screening study showed maximum drug complexation capacity of Kyron T-134. While studying the complexation capacity of resins with Indion 204, 234, 254 and Kyron T-114, T-134, it was found that percentage of drug bound to Kyron T-134 and Indion 234 was more when compared to the percentage of drug bound to Kyron T-114, Indion 254 and Indion 204, as shown in Table 5. Further optimization of complexation capacity of Kyron T-134 and Indion 234 was performed by determining the effect of various factors on complexation process.

**Table 5. Complexation capacity of resin**

| Drug: resin complex ( 1:1) | % Unbound drug | % bound drug |
|---|---|---|
| Indion 204 | 70.59 | 29.41 |
| Indion 234 | 27.48 | 72.52 |
| Indion 254 | 49.68 | 50.32 |
| Kyron T-114 | 45.62 | 54.38 |
| Kyron T-134 | 17.18 | 82.82 |

(a) Effect of soaking time of resin on complexation

Effect of soaking time of resin on complexation showed that, the percentage of drug bound to resin was found to increase as the soaking time for resin increased, as shown in Table 6. But percentage of drug bound to resin was near to constant after 20 min and remained unchanged after 30 min. Hence, soaking time of 30 min was selected for further study.

(b) Effect of stirring time on complexation

Effect of stirring time of resin and drug on complexation showed that, the percentage of drug bound to resin was found to increase as the stirring time increased, as shown in Table 6. A drastic increase in percentage of drug bound to resin was observed from 30 to 60 min but percentage of drug bound to resin was near to constant and remained unchanged after 120 min. Hence, stirring time of 120 min was selected as optimum for further study.

(c) Effect of temperature on complexation

Effect of temperature on complexation showed that, the percentage of drug bound to Indion 234 was 83.89 to 84.69 and percentage drug bound to Kyron T-134 was 94.11 to 95.14, as shown in Table 6. Percentage of drug bound to resin was near to similar at all temperature and no significant difference was observed. So, 30°C temperature was selected for as optimum temperature for further study.

**Table 6. Effect of soaking time, stirring time and temperature on complexation**

| Effect of soaking time of resin on complexation | | | Effect of stirring time of resin and drug on complexation | | | Effect of temperature on complexation | | |
|---|---|---|---|---|---|---|---|---|
| | % bound drug | | | % bound drug | | | % bound drug | |
| Soaking time (Min) | Drug: Indion 234 (1:1) | Drug: Kyron T134 (1:1) | Stirring time ( Min) | Drug: Indion 234 (1:1) | Drug: Kyron T134 (1:1) | Tem (°C) | Drug: Indion 234 (1:1) | Drug: Kyron T134 (1:1) |
| 5 | 54.66 | 59.65 | 30 | 62.34 | 77.81 | 10°C | 83.89 | 94.74 |
| 10 | 63.17 | 71.51 | 60 | 83.54 | 89.36 | 20°C | 84.11 | 94.69 |
| 15 | 70.98 | 77.39 | 90 | 86.12 | 96.74 | 30°C | 84.38 | 94.97 |
| 20 | 72.04 | 84.44 | 120 | 87.24 | 98.75 | 40°C | 84.31 | 95.14 |
| 30 | 72.23 | 84.76 | 150 | 87.08 | 98.54 | 50°C | 84.69 | 94.11 |
| 45 | 73.31 | 84.70 | | | | | | |

(d) Effect of pH on complexation

Effect of pH on complexation showed that, maximum complexation was found between pH 4-6, as shown in Table 7. Below pH 3 and above pH 6, complexation capacity was decreased.

(e) Effect of drug: resin ratio on drug-resin complextion

Effect of drug: resin ratio on complexation capacity showed that, the percentage of bound drug to resin was found to increase with increasing concentration of resin, as shown in Table 7. At 1:0.75 ratio, Kyron T-134 (89.21%) has higher drug binding capacity than Indion 234 (77.81%). Also at 1:1 drug: resin ratio, Kyron T-134 showed higher

binding capacity than Indion 234. So, 1:0.75 and 1:1 drug: Kyron T-134 were considered optimum ratio to load sildenafil in fast dissolving film.

**Table 7. Effect of pH and drug-resin ratio on complexation**

| Effect of pH on complexation | | | Effect of drug-resin ratio on complexation | | |
|---|---|---|---|---|---|
| | % bound drug | | | % bound drug | |
| pH | Drug: Indion 234 (1:1) | Drug: Kyron T134 (1:1) | Drug: Rasin Ratio | Drug: Indion 234 | Drug: Kyron T134 |
| 1.2 | 74.25 | 83.12 | 1: 0.25 | 18.75 | 34.35 |
| 2 | 73.85 | 83.44 | 1:0.5 | 49.57 | 64.85 |
| 3 | 73.84 | 84.11 | 1:0.75 | 77.81 | 89.21 |
| 4 | 84.44 | 90.44 | 1:1 | 84.44 | 98.75 |
| 5 | 84.04 | 94.78 | 1:1.25 | 94.21 | 99.11 |
| 6 | 84.77 | 94.78 | 1.50 | 97.5 | 99.24 |
| 7 | 79.24 | 86.45 | | | |
| 8 | 78.38 | 87.18 | | | |

**Characterization and evaluation of Drug resin complex by IR spectroscopy**

The comparative FTIR spectra of sildenafil citrate, Kyron T-134 and drug-resin complex in 1:0.75 ratio are shown in fig. 5, 6 and 7 respectively. FTIR spectra of sildenafil citrate shows major peaks at 3294 $cm^{-1}$ ( N-H stretching-secondary amine) , a peak at 1358 $cm^{-1}$ ($SO_2$ stretching), a peak at 1697 $cm^{-1}$ (C=O stretch of amide), a peak at 1390 $cm^{-1}$ (-CH3 group terminal, -C–H methyl umbrella band) and a peak at 1170 $cm^{-1}$ ( C-O stretch of ether). FTIR spectra of Kyron T-134 citrate shows major peaks at 1685 $cm^{-1}$ (-C=O stretch of carboxylate), a peak at 3205 $cm^{-1}$ (C-H stretch of aromatic ring ), a peak at 1165 $cm^{-1}$ (-C–O stretch) and a peak at 1395 $cm^{-1}$ (-CH3 group terminal). The absence of sharp characteristic peaks in region of 1685-1697 $cm^{-1}$ and 1358-1395 $cm^{-1}$ in drug-resin complex confirms the complex formation of drug with resin. The peak in region of 3205-3294 $cm^{-1}$ in complex corresponding to N–H stretch (secondary amine) was also absent, which confirms interaction of the amino group of sildenafil citrate and the carboxylic group of the resin.

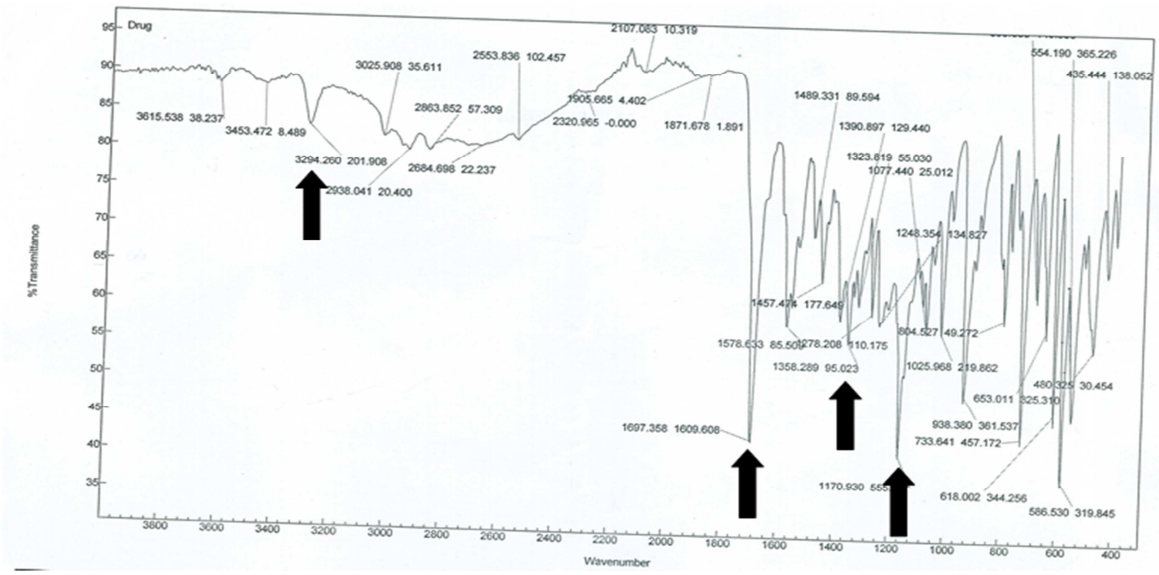


**Figure 5. IR spectra of sildenafil citrate**

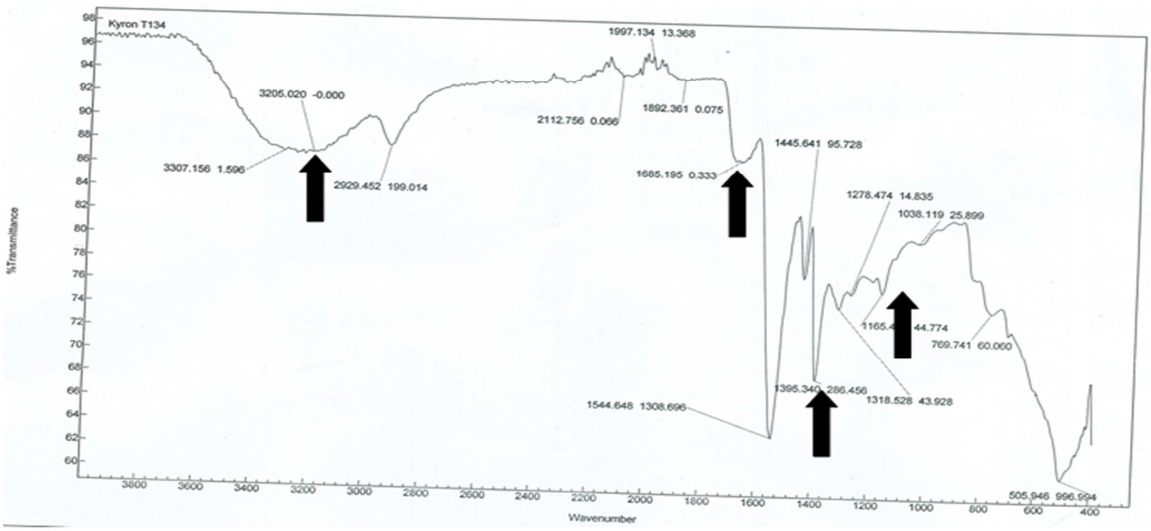


**Figure 6. IR spectra of Kyron T-134**

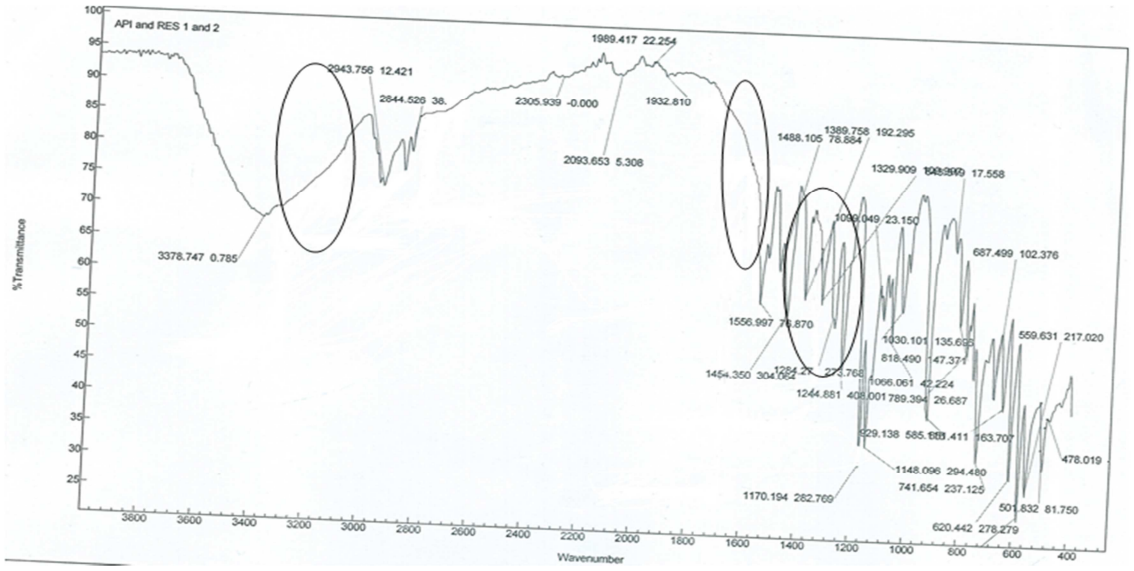


**Figure 7. IR spectra of drug: resin (1: 0.75)**

**Preparation of fast dissolving films containing Sildeanfil citrate**

For taste masking of sildenafil citrate, sildenafil citrate and Kyron T-134 in 1:1 ratio added to formulation. Poor and very brittle film formation was found at 1:1 ratio containing trial F1 and F2, as shown in Table 1. After increasing concentration of plasticizer in trial F2, there was no improvement in tensile strength which might be occurred due to high amount of drug loading per film. So 1: 0.75 drug: resin was taken in trials F3 and F4 but tensile strength of both the batches were not satisfactory which might be due to low polymer strength of HPMC 6 cps. In trial F5 to F7, HPMC E6 was replaced with HPMC E15 as main film former which improved tensile strength and other mechanical property of film but improvement in disintegration time was still required to be optimized. Glycerin as humectants was added to trial F7 to prevent brittleness due to drying and it retains moisture of the film during stability.

**Optimization using $3^2$ full factorial designs and evaluation parameters**

The factorial batches were evaluated for various parameters by the methods described in methodology section. The evaluation results are shown in Table 8. Tensile strength was found in range of 0.110±0.005 to 0.274±0.011 kg/cm2. Folding endurance gives an indication of brittleness of the film. A result showed as the concentration of polymer and plasticizer increases, tensile strength and folding endurance of film increase. Surface pH of all the films prepared was found to be in the range 6.28 to 6.46, which was close to the neutral pH so films may have less potential to irritate the oral mucosa. Thickness was found in the range of 0.08 to 0.18 mm, the different solid content

per unit film of 10.5 $cm^2$ could be the reason for variable thickness of the films. In vitro disintegration time and dissolution time for fast dissolving film was in the range from 12.38 ±0.89 to 33.37 ±2.21and 1.44 ±0.17 to 3.48 ±0.22, respectively. Content uniformity of formulations OT4, OT5, OT6 and OT8 showed better drug content of above 98 %. No significant difference in the drug content among the films indicated good content uniformity. In vitro dissolution study in 900 mL of 0.01N hydrochloric acid was conducted as per method described earlier. The data for in vitro release are shown in Table 9 and are compared in Fig. 8.

**Table 8. Evaluation parameters of $3^2$ factorial design batches**

| Batch code | Tensile strength | Folding endurance | Surface pH | Thickness (mm) | C.U (%) | *In Vitro* D.T. (sec.) | Solution Time (min.) |
|---|---|---|---|---|---|---|---|
| OT1 | 0.110 ±0.005 | 32 ±2.00 | 6.32 ±0.04 | 0.08± 0.02 | 97.21± 0.90 | 12.44± 0.78 | 1.44± 0.17 |
| OT2 | 0.134 ± 0.003 | 39 ± 2.00 | 6.28 ± 0.04 | 0.07 ±0.03 | 96.75 ±0.25 | 12.38 ±0.89 | 1.52 ±0.08 |
| OT3 | 0.137 ±0.010 | 45 ±4.00 | 6.28 ±0.01 | 0.08 ±0.02 | 96.97 ±0.54 | 12.57 ±0.97 | 1.54 ±0.11 |
| OT4 | 0.168 ± 0.003 | 58 ±6.00 | 6.46 ±0.02 | 0.11 ±0.01 | 100.18 ±0.65 | 17.44 ±0.81 | 2.32 ±0.32 |
| OT5 | 0.174 ± 0.004 | 64 ±2.00 | 6.41 ±0.03 | 0.11 ±0.03 | 98.69 ±0.11 | 20.57 ±0.17 | 2.44 ±0.14 |
| OT6 | 0.184 ±0.004 | 67 ±4.00 | 6.46 ±0.01 | 0.12 ±0.02 | 98.57 ±0.89 | 21.34 ±2.09 | 2.52 ±0.07 |
| OT7 | 0.225± 0.002 | 75 ±6.00 | 6.38 ±0.02 | 0.17 ±0.03 | 97.85 ±0.93 | 31.17 ±1.17 | 3.24 ±0.29 |
| OT8 | 0.238± 0.009 | 77 ±2.00 | 6.42 ±0.04 | 0.17 ±0.04 | 99.48 ±0.44 | 31.57 ±0.91 | 3.41 ±0.18 |
| OT9 | 0.274± 0.011 | 91 ±7.00 | 6.46 ±0.04 | 0.18 ±0.03 | 98.11 ±0.21 | 33.37 ±2.21 | 3.48 ±0.22 |

*C.U: content uniformity, D.T: disintegration time. Values are mean ± S.D for 3 determinations*

**Table 9. Results of *in vitro* drug release study of factorial batches**

| Time (min) | %CPR* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | OT1 | OT2 | OT3 | OT4 | OT5 | OT6 | OT7 | OT8 | OT9 |
| 5 | 87.11 ±0.24 | 85.71 ±0.94 | 84.91 ±1.23 | 79.78 ±0.82 | 77.65 ±0.86 | 74.54 ±1.21 | 69.77 ±0.73 | 64.13 ±0.79 | 59.78 ±0.78 |
| 10 | 97.31 ±0.57 | 96.91 ±0.54 | 97.37 ±0.84 | 94.03 ±1.21 | 92.75 ±1.45 | 93.85 ±0.87 | 84.17 ±1.24 | 80.97 ±1.34 | 78.29 ±0.98 |
| 15 | 98.31 ±0.37 | 97.62 ±0.74 | 98.59 ±0.89 | 95.71 ±0.75 | 99.71 ±0.78 | 99.01 ±0.59 | 98.03 ±1.54 | 99.34 ±1.78 | 98.87 ±0.67 |
| 20 | 98.11 ±0.07 | 97.99 ±0.67 | 98.77 ±0.47 | 100.31±0.67 | 99.77 ±0.69 | 100.11±0.09 | 98.45 ±1.78 | 100.12±0.19 | 99.71 ±1.08 |

** Values are expressed as mean ± S.D for three determinations*

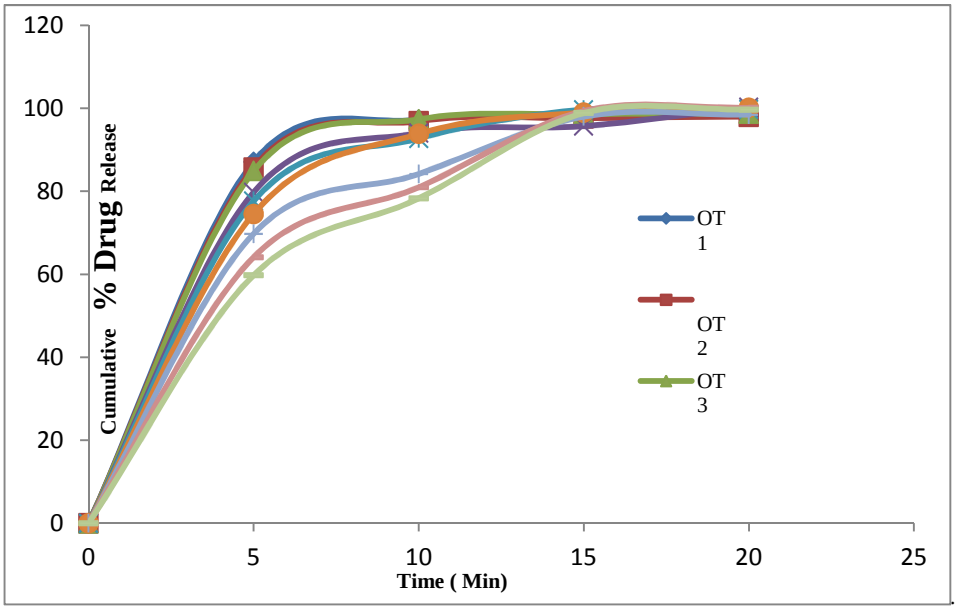


**Figure 8. Drug release comparison of $3^2$ factorial trial batches**

## Statistical analysis of $3^2$ full factorial batches

*Full and reduced model for disintegration time*

The summary of regression analysis and ANOVA for disintegration time is shown in Table 10. 3D surface plot is shown in Fig. 9. From the equation of full model, reduced model is drawn by rejecting insignificant factors on the basis of p value. From the reduced model, it was found that concentration of plasticizer has no significant effect on disintegration time as well as effect of interaction was not found significant. Only concentration of polymer showed significant and positive effect on the tensile strength. As its concentration of polymer increases, disintegration time of film increases.

**Table 10. Summary outputs of regression analysis and ANOVA for disintegration time**

| | DF | SS | MS | F | P-value Prob > F |
|---|---|---|---|---|---|
| Regression | 5 | 594.41 | 118.88 | 95.60 | 0.0017 |
| Residual | 3 | 3.73 | 1.24 | | |
| Total | 8 | 598.14 | | | Significant |
| Coefficient | $b_0$ | $b_1$ | $b_2$ | $b_{11}$ | $b_{22}$ | $b_{12}$ |
| Coefficient value | 19.8622 | 9.7867 | 1.0383 | 2.4667 | -0.1183 | 0.5175 |
| P-value | 0.0002 | 0.0002 | 0.1069 | 0.0521 | 0.8902 | 0.4218 |
| Full Model: $Y_1 = 19.8622 + 9.7867\ X_1 + 1.0383\ X_2 + 2.4667\ X_1^2 - 0.1183\ X_2^2 + 0.5175\ X_1X_2$ | | | | | | |
| Reduced Model: $Y_1 = 19.8622 + 9.7867\ X_1$ | | | | | | |

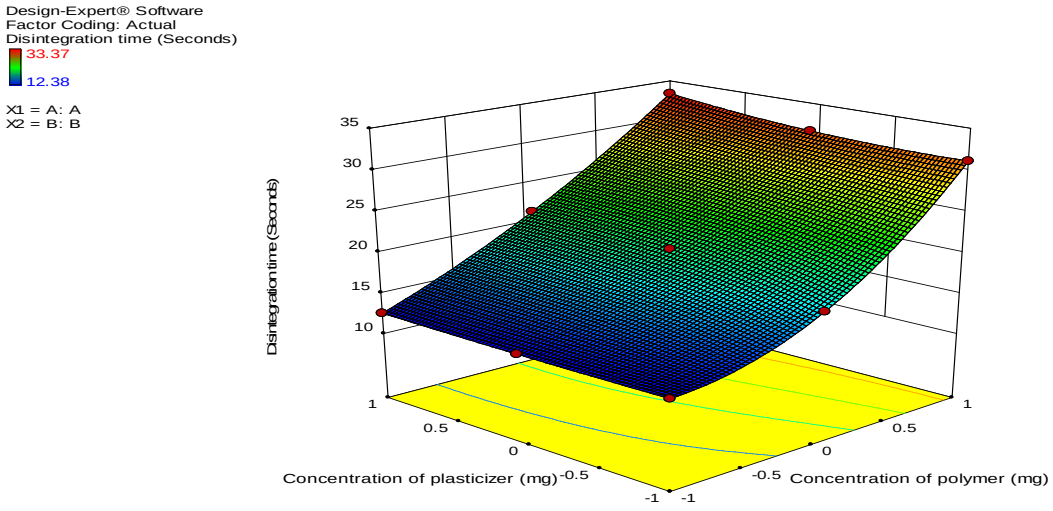


**Figure 9. 3D surface plot of disintegration time**

*Full and reduced model for tensile strength*

The summary of regression analysis and ANOVA for tensile strength is shown in Table11. 3D surface plot is shown in Fig. 10. From the reduced model, it was found that concentration of polymer and plasticizer has significant and positive effect on tensile strength of film but effect of interaction was not found significant. As concentration of plasticizer and polymer increases, tensile strength of film increases.

**Table 11. Summary outputs of regression analysis and ANOVA for tensile strength**

| | DF | SS | MS | F | P-value Prob > F |
|---|---|---|---|---|---|
| Regression | 5 | 0.0229 | 0.0046 | 42.4480 | 0.0055 |
| Residual | 3 | 0.0003 | 0.0001 | | |
| Total | 8 | 0.0232 | | | Significant |
| Coefficient | $b_0$ | $b_1$ | $b_2$ | $b_{11}$ | $b_{22}$ | $b_{12}$ |
| Coefficient value | 0.1747 | 0.0593 | 0.0153 | 0.0110 | 0.0010 | 0.0055 |
| P-value | 0.0002 | 0.0008 | 0.0364 | 0.2311 | 0.9003 | 0.3673 |
| Full Model: $Y_1 = 0.1747 + 0.0593\ X_1 + 0.0153\ X_2 + 0.0110\ X_1^2 + 0.0010X_2^2 + 0.0055X_1X_2$ | | | | | | |
| Reduced Model: $Y_1 = 0.1747 + 0.0593\ X_1 + 0.0153\ X_2$ | | | | | | |

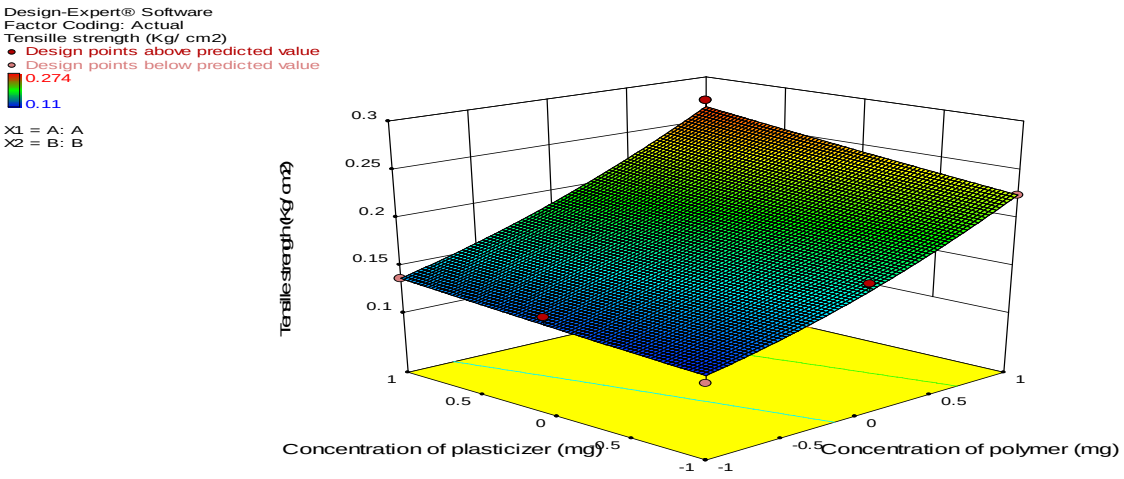


**Figure 10. 3D surface plot of tensile strength**

*Full and reduced model for in vitro drug release at 10 min*

The summary of regression analysis and ANOVA for *in vitro* drug release at 10 min is shown in Table 12. 3D surface plot is shown in Fig. 11. From the model, it was found that concentration of polymer showed negative effect on the *in vitro* drug release. As its concentration increases, *in vitro* drug release decreases. It was concluded that concentration of polymer had the largest effect on the drug release at 10 min, which indicated that polymer retarded the disintegration time of film which ultimately prolonged drug release from film. Concentration of PG showed no significant effect on in vitro drug release at 10 min.

**Table 12. Summary outputs of regression analysis and ANOVA for *In vitro* drug release at 10 min**

| | DF | SS | MS | F | P-value Prob > F |
|---|---|---|---|---|---|
| Regression | 5 | 440.4227 | 88.0845 | 93.9977 | 0.0017 |
| Residual | 3 | 2.8113 | 0.9371 | | |
| Total | 8 | 443.2340 | | | Significant |
| Coefficient | $b_0$ | $b_1$ | $b_2$ | $b_{11}$ | $b_{22}$ | $b_{12}$ |
| Coefficient value | 93.1256 | -8.0267 | -1.0000 | -4.3733 | 0.6267 | -1.4850 |
| P-value | 1.0255E-06 | 0.0003 | 0.0854 | 0.0078 | 0.4274 | 0.0546 |
| Full Model: $Y_1 = 93.1256 - 8.0267\ X_1 - 1.0000\ X_2 - 4.3733X_1^2 + 0.6267\ X_2^2 - 1.4850\ X_1X_2$ | | | | | | |
| Reduced Model: $Y_1 = 93.1256 - 8.0267\ X_1 - 4.3733X_1^2$ | | | | | | |

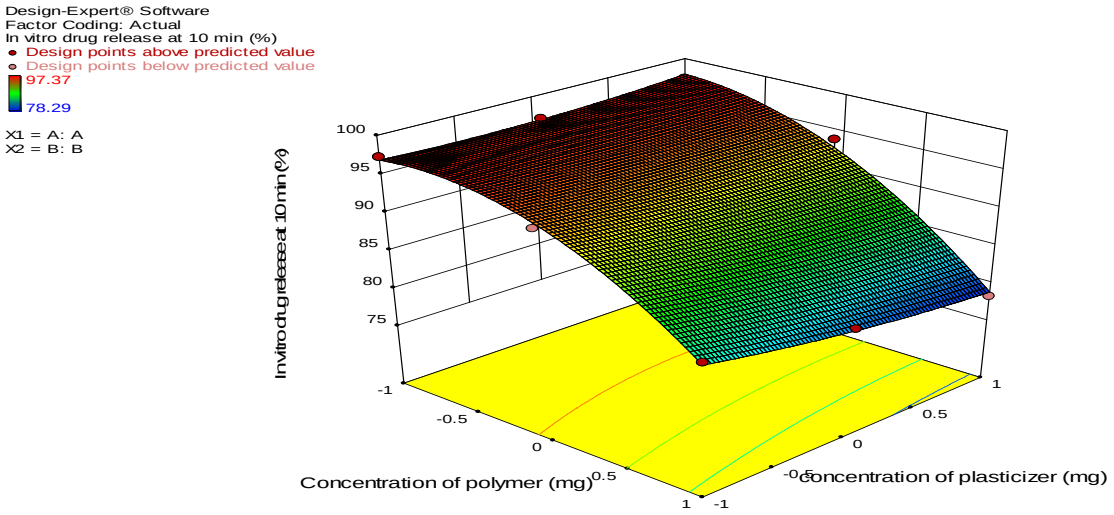


**Figure 11. 3D surface plot of in vitro drug release at 10 min**

*Validation of model by check point batch*

The overlay plot of all factorial batches is shown in Fig. 12. Check point batches C1 and C2 were selected from the overlay plot of responses. The amount of HPMC E15 and Propylene glycol were selected from overlay plot and predicted responses were calculated and are given in the Table 13. Actual response of C1 and C2 batch were measured and compared with the predicted response of check point batches. All the values of responses were within the upper and lower predicted interval. Hence, this model is valid and optimized batch can be selected from the overlay plot of this model.

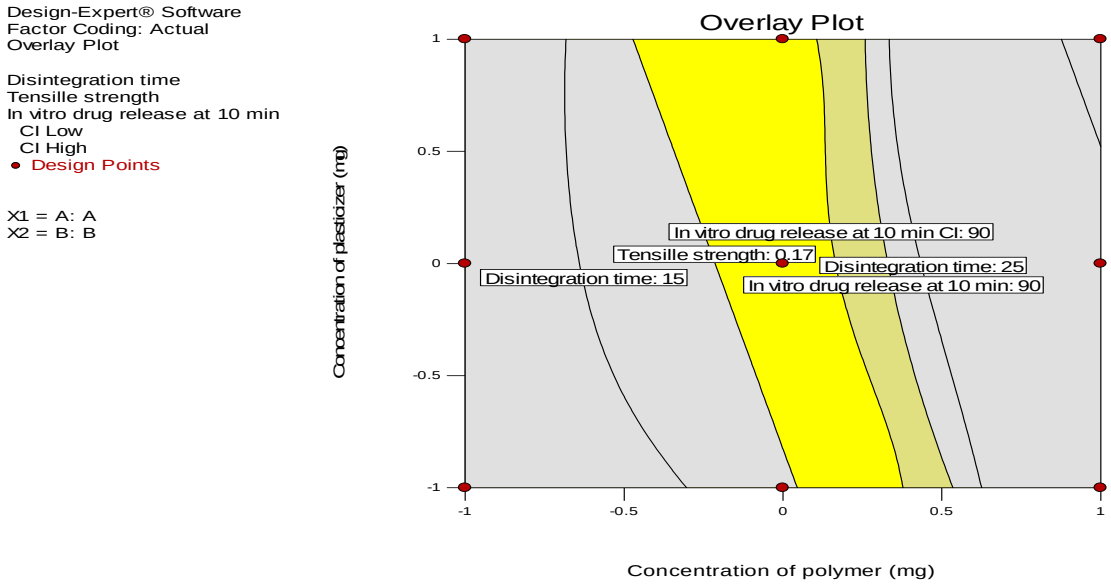


**Figure 12. Overlay plot of $3^2$ full factorial batches**

**Table 13. Predicted and actual responses of check point batches**

| Batches | Values of independent factors from overlay plot | Calculated values of independent Variables ( mg/unit) | Predicted Response | | | Actual Response | | |
|---|---|---|---|---|---|---|---|---|
| | | | D.T. (sec) | % CPR at 10min | Tensile Strength ($kg/cm^2$) | D.T. (sec) | % CPR at 10min | Tensile Strength ($kg/cm^2$) |
| C1 | X1= -0.15142<br>X2= 0.7625 | X1=44.24<br>X2=28.81 | 19.86 | 94.01<br>(92.53, 95.50) | 0.1854 | 21.49 | 92.81 | 0.1770 |
| C2 | X1=0.0690341<br>X2= -0.949148 | X1=45.35<br>X2=20.25 | 18.32 | 94.16<br>(92.54, 95.79) | 0.1722 | 17.51 | 95.11 | 0.1650 |

*Optimization of batch from overlay plot*

From the overlay plot it was seen that batches OT5 and OT6 fall under the optimized area. So, the batch with higher dissolution was considered optimized batch. Thus batch OT6 (Tensile strength: 0.184 kg/ $cm^2$, drug release at 10 min: 93.85 % and Disintegration time: 21.34 sec) was selected as the optimized batch.

**Taste evaluation study by spitting**

The results of the taste evaluation study are presented in Table 3. In this study, mouth feel was ranked as per grittiness and irritability of formulation in mouth. Mean value of mouth feel in both formulations suggested smooth to very smooth feeling. Ease of handling was ranked as per flexibility to take out film from Alu pouch and put it in mouth without need of water which was ranked patient friendly and excellent. In comparison to reference product, test film (optimized formulation OT6) had acceptable to slight sweet taste (Mean 4.00±0.00) and slightly bitter to acceptable after taste (3.88±0.35) and also superior acceptance of formulation.

**Stability Study of Optimized Batch**

The results of stability study at 3 month and 6 month accelerated condition (40ºC ± 2ºC and 75 ± 5% RH), which are shown in Table 14, had shown no significant change in the release profile and other physicochemical property of sildenafil fast dissolving oral film.

**Table 13. Results of accelerated stability study of optimized batch (OT6)**

| Evaluation parameters | Initial | 3 months | 6 month |
|---|---|---|---|
| Physical observation | Light pink colored opaque film | Light pink colored opaque film | Light pink colored opaque film |
| Tensile strength(Kg/cm2) | 0.184 ±0.004 | 0.192 ±0.002 | 0.198 ±0.001 |
| Folding endurance | 67±4.00 | 73 ±4.00 | 78± 2.00 |
| Surface pH | 6.46 ±0.01 | 6.51 ±0.03 | 6.62 ±0.09 |
| In vitro disintegration time (sec) | 21.34±2.09 | 20.37±0.44 | 21.57±0.27 |
| In vitro solution time (Sec) | 2.52 ±0.07 | 3.00 ±0.31 | 3.19 ±0.24 |
| % drug content | 98.57 ±0.89 | 99.41 ±0.12 | 98.60± 0.78 |
| % Drug release at 10 min | 93.85±0.87 | 94.21±0.47 | 94.48±0.31 |

## CONCLUSION

The physical properties like tensile strength, folding endurance etc. were affected by type and concentration of polymer and plasticizer. The optimized formulation (batch OT6) containing HPMC E15 (28.69%), propylene glycol (19.13%) and glycerine (6.38%) showed drug dissolution more than 90% within 10 min with satisfactory taste masking and other physicomechanical properties. Among different taste masking agent, Kyron T-134 was satisfactorily mask the bitter taste of active at drug: Kyron 134 ratio 1:0.75. The development of fast dissolving film of sildenafil is one of the alternative routes to provide quick onset of action. This formulation enhances patient compliance because patient can take it by simply putting it in oral cavity without need of water, 20 min to 30 min before starting activity.

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