International Journal of Chemistry and Pharmaceutical Sciences

Journal Home Page: www.pharmaresearchlibrary.com/ijcps

Research Article **Open Access**

Formulation and Evaluation of Avanafil Orodispersible Tablet

Anuradha Patel*, Ajay Nair, Parixit Prajapati, Dr. Anil Jadhav

Department of Pharmaceutics, Smt. B.N.B Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India.

A B S T R A C T

The aim of this study is to improve the solubility and oral bioavailability of Avanafil a recently approved second generation type 5 phosphodiestrase inhibitor used for the treatment of erectile dysfunction by employing cyclodextrin complexation technique. The inclusion complex was prepared by Kneading method. Differential scanning calorimetry, X-ray powder diffraction, and Fourier transform infrared spectroscopy is used to evaluate the complexation of Avanafil with hydroxypropyl-β-cyclodextrin (HP-β-CD) and the formation of true inclusion complexes. The inclusion complex containing Avanafil and Hydroxypropyl β-Cyclodextrin (1:1 molar ratio) is formulated into Orodispersible tablet by direct compression method using different superdisintegrant i.e. Croscarmellose, Crospovidone and Sodium Starch Glycolate. A 3^2 full factorial design was applied to systematically optimize the drug disintegration time. The concentration of Sodium Starch Glycolate (X1) and concentration of Croscarmellose sodium (X2) were selected as independent variables. The Disintegration time (Y1) and Wetting time (Y2) were selected as dependent variables. The prepared tablets will be evaluated for various post compression parameters like hardness, friability, disintegration time, wetting time, weight variation, thickness, drug content and in-vitro dissolution. Regression analysis and numerical optimization were performed to identify the best formulation. Formulation F10 prepared with Starch Glycolate (14.83%) & croscarmellose (8.09%) was found to be the best formulation with disintegration time 21 sec, wetting time 27 sec and % drug release in 10 min 97.45%.

Keywords: Avanafil, Orodispersible tablet, Hyroxy propyl beta cyclodextrin, Sodium strach glycolate, Croscarmellose sodium, Disintegration time, Wetting time, Full factorial design

A R T I C L E I N F O

CONTENTS

Article History: Received 06 July 2015, **Accepted** 29 August 2015, **Available Online** 27 September 2015

***Corresponding Author**
Anuradha Patel
Department of Pharmaceutics,
Smt. B.N.B Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India.
Manuscript ID: IJCPS2691

PAPER-QR CODE

Citation: Anuradha Patel, et al. Formulation and Evaluation of Avanafil Orodispersible Tablet. *Int. J. Chem, Pharm, Sci.*, 2015, 3(9): 1975-1986.

1. Introduction

The oral route of administration is considered as the most widely used route. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient incompliance particularly in case of pediatric and geriatric patients. Of all the orally administered dosage forms, tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing. Because of changes in various physiological functions associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy. The pediatric and geriatric patients are of particular concern. Thus a new delivery system known as rapidly dissolving or disintegrating dosage forms is gaining importance. These systems dissolve rapidly in saliva and can be swallowed without the need of water. [1, 2, 3]

Avanafil is highly selective second generation type 5 phosphodiesterase inhibitor used for the treatment of erectile dysfunction which was recently approved by US Food and Drug Administration on on April 27, 2012. Avanafil have faster onset of action as well as higher specificity for phosphodiesterase type 5 inhibitors with fewer side effects in comparision of other oral phosphodiesterase type 5 inhibitors drugs. Concomitant food intake does not affect the absorption of avanafil compared with sildenafil and vardenafil. Potential advantages of this drug include once-or twice daily dosing of avanafil does cause significant drug accumalation in the body. [6]

Avanafil belongs to the BCS class II drug so the rate limiting step in absorption of drug is dissolution rate. To improve the solubility and dissolution rate of avanafil it is prepared by inclusion complex with hydroxypropyl β cyclodextrin. Solid Avanafil–Hyroxy propyl β cyclodextrin inclusion complex were prepared using kneading method. DSC and FTIR were used to evaluate the physicochemical properties of the prepared systems in order to clarify any interaction between the drug and the used carriers. In-vitro dissolution studies of all the prepared systems were carried out to investigate the effect of the molar ratio, on Avanafil dissolution. Orodispersible tablet of Avanafil–Hyroxy propyl β cyclodextrin inclusion complex were prepared by direct compression technique using different super disintegrants. Full factorial experimental design is one of the best tools for studying the effect of different variables on the quality determinant parameters of any formulation. Multiple regression analysis of results gives an equation that adequately describes the influence of the independent formulation variables on the selected responses.

2. Materials and Methods

Avanafil was obtained from OM Laboratories Ahmedabad. Hydroxypropyl β cyclodextrin, Cross carmellose sodium, Crospovidone, Sodium Starch Glycolate and other excipients samples are obtained from Vishal chem. Mumbai. Mannitol sample is obtained from Lobachemi.

Methods

Spectroscopic Analysis of Avanafil: [14, 15]

Preparation of Stock solution: Standard drug solution of Avanafil was prepared by dissolving 10 mg Avanafil in little quantity of HCL buffer pH 1.2 and volume was made up to 100ml with the same solution to obtain stock solution of 100µg/ml concentration. Further stock solution was diluted suitably to get 10 µg/ml solution.

Determination of λmax:

The standard stock solution of Avanafil (10µg/ml) was analyzed using UV-visible spectrophotometer and absorption maximum (λmax) was found to be 248 nm.

Preparation of working solution:

From stock solution (100 µg/ml), accurately measured standard working sample solutions of Avanafil (0.2, 0.4, 0.6, 0.8,and 1ml) were transferred to a series of 10 ml of volumetric flasks and diluted to the mark with HCL buffer pH-1.2 to obtain the concentration of 2, 4, 6, 8, 10 µg/ml . The absorbance of prepared solutions of Avanafil in HCL Buffer pH-1.2 was measured at 248 nm using UV-visible spectrophotometer against HCL buffer pH-1.2 as blank. The experiment was performed in triplicate and based on average absorbance; the equation for the best line was generated.

Drug and Excipients Compatibility Study:

Compatibility study of Avanafil with excipient to be used with it: Physical mixtures of Avanafil were prepared by mixing drug with Excipients in 1:1 ratio. These samples were subjected to compatibility studies and stored for 2 weeks at elevated temperature and humidity conditions of 40±2 ˚C /75±5 % RH. FTIR spectra of these stored samples were then obtained after 2 weeks.

Formulation Development:

Solubiity Enhancement of Avanafil by Hydroxy propyl β-Cyclodextrin [10, 11]: Inclusion complex of Avanafil with hydroxypopyl-β-cyclodextrin were prepared by kneading method. Calculated amount of Avanafil and hydroxypopyl-β-cyclodextrin was triturated in a mortar with a small volume of water –methanol (1:1 v/v) solution. The thick slurry that formed was kneaded for 45 min and then dried at 45 °C. The dried mass was sieved through sieve no. 60. Store in cool place and in air tight container.

Table 1: Inclusion Complex of Avanafil with hydroxypopyl-β-cyclodextrin

Inclusion Complex Proportions (Molecular Weight Ratio)	
Avanafil	**Hydroxy propyl β-Cyclodextrin**
1	0.50
1	1
1	2

Saturation Solubility Study:

The shake flask method was used to determine saturation solubility of Complex. Excess quantity of complex were added in 10 ml Water which were then mixed in vortex mixture at 37°C and at 100 rpm for 24 h. Solutions were filtered using Whatman filter paper. The filtrates were

diluted suitably and solutions were analyzed using UV-visible spectrophotometer at 200 to 400 nm. Then calculate the solubility of complex.

Physicochemical characterization of Avanafil–HPβCD inclusion complex:

DSC thermograms, FT-IR spectra were recorded for pure Avanafil, pure HPβCD, and inclusion complex.

Differential scanning calorimetry (DSC):

The DSC thermogram of Avanafil and inclution complex containing hydroxypropyl β cyclodextrin were recorded using Differential scanning calorimeter with liquid nitrogen cooling accessory. Approximately 2 to 5 mg of sample was heated in a closed pierced aluminum pan from 45 °C to 345 °C at a heating rate of 10 °C/min under a stream of nitrogen at a flow rate of 50 ml/min.

Fourier Transform Infrared spectroscopy (FT-IR):

The samples of Avanafil, HPβ-CD and inclusion complexes were prepared in the form of KBr pellets and subjected for scanning from 4000 cm-1 to 400 cm-1 using FT-IR spectrophotometer.

Drug content:

An accurately weighed quantity of inclusion complex equivalent to 50 mg of Avanafil was taken into a 100ml volumetric flask and dissolved in small amount of 0.1N HCL and filtered through a whatman No. 1 filter paper. The filtrates were diluted suitably with 0.1 N hydrochloric acid (HCl) solution of pH 1.2. The content of Avanafil was determined spectrophotometrically at 248 nm against suitable blank using UV-visible spectrophotometer.

***In-vitro* dissolution studies of Avanafil-HPβ-CD complex:**

The quantity of inclusion complex equivalent to 50 mg of Avanafil was placed in dissolution medium. The dissolution study of complex was conducted using dissolution testing apparatus II (paddle method) in 900 ml of distilled water solution of pH 1.2 at 37±0.5ºC and at a speed of 100 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 248 nm against suitable blank using UV-visible spectrophotometer. Dissolution profile of Avanafil was also carried in similar manner.

Preparation of Avanafil Orodispersible Tablet:

Orodispersible tablets were prepared by direct compression method according to formula given in the Table 1. Nine different formulations were prepared. All the ingredients were sieved separately through sieve no. 40 except magnesium stearate which was sieved throughsieve no. 60 and collected. The weighed amountof inclusion complex equivalent to 50 mg of drug and other ingredients were mixed first and magnesium stearate was finally added and mixed thoroughly. The tablets were compressed by a 8 mm diameter punch with the help of a rotary tablet compression machine.

Preliminary study: [16, 17]

Selection of super disintegrating Agent:

In preliminary trial batches, Orodispersible tablet were prepared by direct compression using different superdisintegrant i.e. Sodium starch glycolate (SSG), Crospovidone (CP), Croscarmellose sodium (CCS). The prepared tablets were evaluated for various parameters like weight variation, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time and in vitro dissolution depending upon the results obtained Crosscarmellose and Sodium strach glycolate were selected and subjected for further investigation.

Experimental Design: [16, 17]

Full Factorial Design: A 3^2 randomized full factorial design was adopted to optimize the variables. In the design, 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amount of superdiintegrating agent (sodium strach glycolate, X1) and (Crosscarmellose sodium, X2) were chosen as independent variables. The disintegration time (DT) and Wetting time (WT) were selected as dependent variables. Batches of factorial design were shown in Table-4.

Evaluation Parameters of Avanafil orordispersible tablets:

A) Pre-Compression parameters: [3, 4, 5]

Orally disintegrating tablets are manufactured by several processes but for all of them, first a blend of various ingredients (APIs and excipients) is made.The quality of tablet, formulated is generally depending upon the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested are as given below.

1. Bulk density:

Bulk density of the granules was determined by pouring gently 10g of sample through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density will be calculated as follows:

Bulk Density (g/ml) = Weight of sample in grams/ volume occupied by the sample

2. Tapped Density:

10 grams of granule sample was be poured gently through a glass funnel into a 50ml Graduated cylinder. The cylinder will be tapped from height of 2 inches until a constant volume will be obtained. Volume occupied by the sample after tapping will be recorded and tapped density will be calculated as follows:

Tapped Density (g/ml) =Weight of sample in grams/Volume occupied by the sample.

3. Carr's Index: One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index, I, which is determined by the following equation**,**

I = Tapped density − Bulk density/Tapped density × 100.

4. Hausner's ratio:

Hausner's ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability. Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula.

Hausner s ratio =Tapped density/Bulk density

5. Angle of repose:

Angle of repose (θ) is a measure of flowability of material. It was determined using fixed height funnel method. A glass funnel was placed with its tip positioned at a fixed height (h) above a graph paper on a horizontal surface. The blend was poured through a funnel until the apex of conical pile touched the tip of the funnel. The radius of the pile (r) was measured and angle of repose was calculated as follows.

θ = tan-1 (h/r)

Where,

θ = angle of repose

h = height of the pile

r = average radius of the powder cone

B) Post-Compression Parameters: [3, 4, 5]

1. Weight Variation:

The weight of the tablet is routinely measured to ensure that the tablet contains proper Amount of drug. 20 tablets were taken at random for the test and were weighed, individually and the average weight was calculated. The % deviation of each tablet from the average weight was calculated.

% Weight variation = (Average weight-Individual weight) / Individual weight × 100

2. Hardness:

Tablets require a certain amount of strength, or hardness, to withstand the mechanical shocks of handling in manufacturing, packaging as well as in shipping. The hardness of the tablets here was measured using a simple Monsanto hardness tester. In this, a tablet is placed between the plungers, and was tightened from one end, and pressure required to break the tablet diametrically was measured.

3. Friability:

In this test 10 tablets was weighed and placed in a Roche Friabilator test apparatus, and then the tablets was subjected to rolling and repeated shocks, resulting from free falls within the apparatus from the height of 6 inches. After 100 revolutions the tablets will be removed, de-dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Loss = (Initial weight-Final weight) / Initial weight ×100

4. Dimensions:

The thickness and diameter of the tablets was determined using a vernier caliper. Five tablets from each formulation were used and average values were calculated.

5. Wetting time & Water Absorption Ratio (%):

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of purified water. A tablet was put on the paper, and the time required for complete wetting was measured. Six trials for each batch were performed; average time for wetting with standard deviation was recorded. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation,

R = 100 (Wa-Wb)/ Wb

Where,

Wa and Wb are the weight after and before water absorption, respectively. The average value with standard deviation was recorded.

6. Drug content uniformity:

10 tablets were weighed and triturated. The tablet triturate equivalent to 50 mg of the drug was weighed accurately, dissolved in 0.1N HCl and suitably diluted with 0.1 N hydrochloric acid (HCl) solution of pH 1.2. The content of Avanafil was determined spectrophotometrically at 248 nm against blank using UV-visible spectrophotometer

7. *In vitro* disintegration time:

In-vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The water was maintained at a temperature of 37±0.5ºC and time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

***8. In vitro* dissolution studies of prepared tablet:**

In-vitro dissolution study was performed by using USP dissolution testing apparatus II (Paddle method). Weighed tablets from different batches were kept in a flask of the apparatus containing 900 ml of 0.1 N hydrochloric acid (HCl) solution of pH 1.2 dissolution medium, maintained the temperature at 37±0.5ºC and at a speed of 50 rpm. Aliquot of dissolution medium (10 ml) was withdrawn at specific time intervals and the samples were replaced with fresh dissolution medium. Aliquot were analyzed spectrophotometrically at 248 nm against suitable blank using UV-visible spectrophotometer.

3. Results and Discussion

Calibration curve of Avanafil in 0.1 N HCl buffer pH 1.2:

Avanafil exhibits maximum absorbance at 248 nm in 0.1 N HCl buffer pH 1.2 in the range of 2-10 µg/ml. The results of calibration curve preparation are shown in Table 5

Interpretation:

To study the compatibility of drug with excipients IR spectra of drug in combination with excipients in 1:1 ratio was studied prior to preparation of Avanafil orally disintegrating tablets. FTIR spectra of Avanafil show characteristic bands are attributed to the stretching of different group vibrations The IR spectrums of Avanafil and its combination with Sodium Starch Glycolate, Croscarmellose, etc. were shown in Figures 5, 6 indicate that there was no physicochemical interaction in between drug and studied excipients because all characteristics bands were presented inphysical mixture.

Formulations and Development:

Considering all experiments Avanafil and Hydroxy propyl β–Cyclodextrin in Proportion of **1:1** was shown 8 times increases in Solubility of Pure Avanafil. The ratio 1:1 is utilized because tablet dose can be set within the range of Orodispersible tablet and its value of increase in solubility is nearer to 1:2 ratios and it is cost effective.

7.2Differential scanning calorimetry (DSC):

The DSC spectra of Avanafil (A) and inclusion complex containing hydroxyl propyl-β- cyclodextrin prepared by kneading method are depicted in Fig. 7. The DSC thermogram of Avanafil was typical of a crystalline substance, exhibiting a sharp endothermic peak at 163.71^0C, corresponding to the melting point of the drug. The drug endothermic melting peak completely disappeared

in the DSC thermograms of the inclusion complex prepared using HP-β-CD. This could indicate amorphous solid dispersion or molecular encapsulation of the drug into the cyclodextrin cavity.

Dissolution Rate of Drug from Hydroxy propyl β–Cyclodextrin:

The complex was subjected to dissolution studies in distilled water using USP type II apparatus at 100 rpm and 37 ± 0.5 °C. The Figure 8 shows that drug release was more than 80% within 30min.

Evaluation of taste of Avanafil inclution complex with hydroxy propyl β cyclodextrin:

The taste masked Avanafil inclution complex with hydroxy propyl β-cyclodextrin was given to a panel of healthy human volunteers for taste masking evaluation using time intensity method. As we know the time of ODTs in the oral cavity is around 1 minute or less.

Evaluation of Granules:

The prepared granules were evaluated for the blend property like bulk density, tapped density, Carr's index, Hausner ratio and angle of repose. Results obtained were as shown in Table 8 below. The granules for all nine formulations were evaluated for bulk density which ranged from 0.285to 0.326, Carr's index ranged from 5 to 28 and angle of repose ranged from 25º.08' to 29º.06'. All these results indicate that, the granules possess satisfactory flow and compressibility properties.

Tablet weights in all the 9 batches varied between 178 to 180 mg. All the formulated (F1 to F9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ± 7.5%.Thickness of all tablets was in the range between 2.3 mm to 2.4 mm. Hardness of tablets was in range between 3.3 to 3.4 kg/cm2.Friability was in range between 0.42 to 0.68 %.Thus, all the physical parameters of the manually compressed tablets were quite within control. Friability values were less than 1 % in all cases shows good mechanical strength at the time of handling and transports. The % drug content for tablets of all formulation was found to be in the range of 98.23 to 99.78%. Thus the assay of Avanafil was found to be quite within the range.

The results shown in Table 10 indicated that concentration-dependent disintegration was observed in batches prepared using combination of SSG and CCS. As SSG combined with CCS, by keeping concentration of SSG constant and increase concentration of CCS from 4 to 12%, disintegration time was decreased as shown in result. The wetting time of tablets as shown in Table 2 of all nine formulations was in the range of 26 to 64 seconds. The wetting time is closely related to the disintegration time.

The dissolution profiles of all the nine formulations are shown in Figure .From graph it was concluded that as the concentration of super disintegrant increases, % drug release was also increased. % drug release from F8 and F9 formulations prepared with SSG 15 % and CCS 8% and12 % was shown 97.50% and 98.40 % in 10 minutes. Combination of two disintegrates also improves dissolution rate as compared to individual super disintegrant. The release of drug was largely depended on the disintegration

Data Analysis:

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis. The disintegration time and wetting time were selected as dependent variables. The polynomial equations (full and reduced) relating the responses, disintegration time and wetting time to the transformed factor are described below. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive). Table 8 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Since the values of r^2 are quite high for all the two responses, i.e., 0.9955 to 0.9950, the polynomial equations form excellent fits to the experimental data and are highly statistically valid.

Factorial equation for Dependent Variables

1) Factorial equation for Disintegration Time:

Y= 27.11 – 10.50 X1 -7.33X2 +2.00 X1X2 +4.83 X12 + 6.33 X22, R2= 0.9955

Positive sign in front of terms indicate synergistic effect while negative indicate antagonistic effect upon responses. So, sign of b1 andb2 were negative shows that as a concentration of SSG and CCS increases , DT decreases. As the R2 value nearer to 1 indicate selected model was significant.

2) Factorial equation for Wetting Time:

Y= 33.00 -10.50 X1 -8.00 X2 +2.00 X1X2 +4.50X2 +7.00 X22, R2= 0.9950

Positive sign in front of terms indicate synergistic effecy while negative indicate antagonistic effect upon responses. So, sign of b1 andb2 were negative shows that as a concentration of SSG and CCS increases, WT decreases. As the R2 value nearer to 1 indicate selected model was significant.

ANOVA for Quadratic Model for DT and WT:

ANOVA table used to generate mathematical models. The high values of correlation coefficient for DT and WT indicate a good fit i.e.good agreement between the dependent and independent variables. The mathematical model was evolved by omitting insignificant term ($p>0.05$). So, the main effect X1 & X2 were found significant as p value was < 0.05.

The dissolution profiles of all the nine formulations are shown in Figure .From graph it was concluded that as the concentration of super disintegrant increases, % drug release was also increased. % drug release from F8 and F9 formulations prepared with SSG 15 % and CCS 8% and12 % was shown 97.50% and 98.40 % in 10 minutes. Combination of two disintegrates also improves dissolution rate as compared to individual super disintegrant. The release of drug was largely depended on the disintegration

Data Analysis: The statistical analysis of the factorial design batches was performed by multiple linear regression analysis. The disintegration time and wetting time were selected as dependent variables. The polynomial equations (full and reduced) relating the responses, disintegration time

and wetting time to the transformed factor are described below. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive). Table 8 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Since the values of r^2 are quite high for all the two responses, i.e., 0.9955 to 0.9950, the polynomial equations form excellent fits to the experimental data and are highly statistically valid.

Factorial equation for Dependent Variables:

1) Factorial equation for Disintegration Time

Y= 27.11 – 10.50 X1 -7.33X2 +2.00 X1X2 +4.83 X12 + 6.33 X22, R2= 0.9955: Positive sign in front of terms indicate synergistic effect while negative indicate antagonistic effect upon responses. So, sign of b1 andb2 were negative shows that as a concentration of SSG and CCS increases, DT decreases. As the R2 value nearer to 1 indicate selected model was significant.

2) Factorial equation for Wetting Time:

Y= 33.00 -10.50 X1 -8.00 X2 +2.00 X1X2 +4.50X2 +7.00 X22, R2= 0.9950: Positive sign in front of terms indicate synergistic effecy while negative indicate antagonistic effect upon responses. So, sign of b1 andb2 were negative shows that as a concentration of SSG and CCS increases, WT decreases. As the R2 value nearer to 1 indicate selected model was significant.

ANOVA for Quadratic Model for DT and WT:

ANOVA table used to generate mathematical models. The high values of correlation coefficient for DT and WT indicate a good fit i.e.good agreement between the dependent and independent variables. The mathematical model was evolved by omitting insignificant term ($p>0.05$). So, the main effect X1 & X2 were found significant as p value was < 0.05.

Optimization of formulation ingredients:

Validation of 3^2 Full Factorial Design is necessary for confirmation of applied model. Check point batch F10 contains 14.83 % of Sodium starch glycolate and 8.09% of croscarmellose was formulated and evaluated for different physicochemical parameter to validate the design. From the full factorial model, it is expected that the Disintegration time and Wetting time of the check point batch should be 21.36 and 26.92 sec respectively. Table 14 indicates that the results are as expected. Thus, we can conclude that the statistical model is mathematically valid.

4. Conclusion

From the results obtained, it can be concluded that complex of Avanafil with Hydroxypropyl ß cyclodextrin improved the solubility and dissolution behaviour of Avanafil. Tablets prepared with sodium starch glycolate and croscarmellose showed less disintegration time compared to crospovidone. Thus concentration of sodium starch glycolate and concentration of croscarmellose was selected as independent variable. From the results of 3^2 full factorial design revealed that amount of sodium starch glycolate and amount of croscarmellose significantly affect the dependent variables, disintegration time and wetting time. It is thus concluded that by using response surface design, an optimum point can be reached in the shortest time with minimum efforts. The derived polynomial equation and contour plots aid in predicting the values of selected independent variables for the preparation of optimum Avanafil or dispersible tablets with desired properties.

Table 2: Composition of Preliminary batches of tablet

SR.NO	Ingredients(mg)	T1	T2	T3	T4	T5	T6	T7	T8	T9
1	Inclusion complex containing 5omg of Avanafil	100	100	100	100	100	100	100	100	100
2	Sodium starch glycolate	4	8	12	-	-	-	-	-	-
3	Crospovidone	-	-	-	4	8	12	-	-	-
4	Crosscarmellose sodium							4	8	12
5	Microcrystalline cellulose	10	10	10	10	10	10	10	10	10
6	Aspartame	3	3	3	3	3	3	3	3	3
7	Talc	4	4	4	4	4	4	4	4	4
8	Magnesium stearate	2	2	2	2	2	2	2	2	2
9	Mannitol QS	57	53	49	57	53	49	57	53	49
	Total weight(mg)	180	180	180	180	180	180	180	180	180

Blank space (dace) indicate that those components not present in the formulations

Table 3: Coded Factor Level of selected super disintegrant's

Coded factors	Levels	Actual value	
		SSG (%)	CCS (%)
-1	Low	5	4
0	Intermediate	10	8
1	High	15	12

Table 4: Design Layout of factorial design batches

SR.NO	Ingredients(mg)	B1	B2	B3	B4	B5	B6	B7	B8	B9
1	Inclusion complex containing 50mg of Avanafil	100	100	100	100	100	100	100	100	100
2	Sodium starch glycolate	5	5	5	10	10	10	15	15	15
3	Crosscarmellose sodium	4	8	12	4	8	12	4	8	12
4	Microcrystalline cellulose	10	10	10	10	10	10	10	10	10
5	Aspartame	3	3	3	3	3	3	3	3	3
6	Talc	4	4	4	4	4	4	4	4	4
7	Magnesium stearate	2	2	2	2	2	2	2	2	2
8	Mannitol QS	52	48	44	47	43	39	42	38	34
	Total weight(mg)	180	180	180	180	180	180	180	180	180

Table 5: Concentration and absorbance of Avanafil in 0.1 N HCl buffer pH 1.2

Concentration(µg/ml)	Absorbance(mean ± SD) (n=3)
0	0
2	0.181 ± 0.001
4	0.328 ± 0.002646
6	0.501 ± 0.002
8	0.651 ± 0.002082
10	0.824 ± 0.002

Table 6: IR Interpretation

Group	Wave number (cm^{-1}) present in IR spectra of drug	Specified range (cm^{-1})
-OH stretching	3248.65	3000-3700
-C=O stretching of amide	1638.38	1600-1900
-N=N	1590.55	1500-1700
C-H bond weakened aldehydic	1325	1300-1500
C-O stretch of anhydride linkage	1061.47	1350-1050
-C-Cl stretch	800.20	600-800

Table 7: Solublity Enhancement of Avanafil by Hydroxy propyl β-Cyclodextrin

Avanafil:Hydroxy propyl β- Cyclodextrin Proportion (M.W. Ratio)	Complex Solubility	Pure Avanafil Solubility	Increased Solubility
1:0.5	0.064		3.2
1:1	0.16	0.02mg/ml	8
1:2	0.17		8.5

Table 8: Taste Evaluation of Avanafil inclution complex with hydroxypropyl β cyclodextrin

Volunteer	BITTERNESS LEVEL AFTER		
	10 sec	30 sec	1mins
1	X	X	0
2	X	0	0
3	X	X	0
4	X	0	0
5	X	0	0

3-Strong bitterness, 2-Moderate bitterness, 1-Slight bitterness, X-Threshold bitterness, 0 –No bitterness.

Table 9: Pre-Compression Evaluation Parameters of Powder Blend of Factorial Batches

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's Ratio	Carr's index	Angle of repose (^{0})
F1	0.312± 0.14	0.400± 0.14	1.28± 0.11	22 ± 2.32	29º.06'± 0.04
F2	0.326± 0.11	0.442± 0.33	1.35 ± 0.63	18± 0.11	27^o.67'± 0.11
F3	0.322 ± 0.63	0.450± 0.04	1.39±0.36	28±0.36	26^o.85'± 0.24
F4	0.294± 0.33	0.312± 0.11	1.06± 0.14	5± 0.04	27º.78' ± 0.63
F5	0.303 ± 2.32	0.322±0.36	1.06± 0.33	5.9± 0.33	26º.08'±'0.36
F6	0.310± 0.04	0.333 ± 2.32	1.07 ± 0.63	6± 0.24	25º.08'± 0.14
F7	0.290 ± 0.63	0.320± 0.11	1.10± 0.14	9± 0.14	28º.67'± 0.11
F8	0.285± 0.11	0.326 ± 0.63	1.0 ± 2.32	12.5± 0.24	27º.55' ± 0.63
F9	0.306±0.36	0.357± 0.14	1.16± 0.11	14.2 ± 0.63	27º.08±'0.36

All values are expressed as mean ± standard deviation, n=3

Table 10: Evaluation parameters of Orodispersible tablets of factorial batches F1toF9

Formulation	Weight variation (mg)±SD, n=20	Hardness (Kg/cm2) ±SD	Thickn ess (mm) ±SD	Water Absorption ratio % ±SD	Friability (%)±SD	Drug content (%)± SD
F1	179 ±1.14	3.4±0.12	2.3±0.02	92.50±2.650	0.61± 0.06	99.48±1.23
F2	179±0.85	3 .4 ±0.10	2.3±0.01	89.60±1.638	0.58± 0.12	99.21±1.12
F3	179 ±1.14	3.3 ± 0.15	2.4±0.02	85.40±1.189	0.52± 0.11	99.67±1.49
F4	178 ±1.48	3.3 ± 0.10	2.4±0.02	93.50±1.077	0.45± 0.04	98.32±1.56
F5	179 ±0.94	3.3±0.12	2.4±0.02	87.70±0.838	0.59± 0.12	98.53±1.39
F6	179 ±1.70	3.3±0.15	2.4±0.02	93.40±0.630	0.68± 0.02	98.56±1.43
F7	180 ±1.66	3.3 ± 0.12	2.3±0.03	85.80±1.189	0.42± 0.04	99.14±0.87
F8	179 ±1.52	3.3±0.17	2.3±0.01	89.30±1.177	0.54± 0.08	99.78±1.32
F9	180 ±1.79	3.3±0.12	2.3±0.01	92.40±1.480	0.63± 0.12	98.23±1.67

All values are expressed as mean ± standard deviation, n=3

Table 11: Factorial Design Layout and Data Transformation for Factorial Batches

Run	Independent Variables in coded form		Independent Variable in actual form		Dependent variable	
	Factor 1	Factor 2	Sodium starch glycolate	Cross carmalose sodium	Disintegration time(sec) ±SD	Wetting time(sec) ±SD
1	-1	-1	5	4	58± 1.527	64±0.577
2	-1	0	5	8	43± 1.000	49± 0.577
3	-1	1	5	12	39± 0.577	45± 1.155
4	0	-1	10	4	40± 1.155	49± 1.527
5	0	0	10	8	31± 1.527	33± 0.577
6	0	1	10	12	26± 0.577	31± 2.082
7	1	-1	15	4	34±2.083	40± 1.527
8	1	0	15	8	20±1.527	26±1.155
9	1	1	15	12	23± 1.155	29±1.000

Table 12: ANOVA Response Surface Quadratic Model for Disintegration Time

Source	SS	df	MS	F Value	p-value prob > F	R^2
Model	1127.11	5	225.42	132.21	0.0010	
A –SSG	661.50	1	661.50	388.27	0.0003	
B –CCS	322.67	1	322.67	189.39	0.0008	
AB	16.00	1	16.00	9.39	0.0548	**0.9955**
A2	46.72	1	46.72	27.42	0.0136	
B2	80.22	1	80.22	47.09	0.0063	
Cor Total	1132.22	8	-	-	-	

Table 13: ANOVA Response Surface Quadratic Model for Wetting Time

Source	SS	df	MS	F Value	p-value prob > F	R^2
Model	1200.00	5	240.00	120.00	0.0012	
A –SSG	661.50	1	661.50	330.75	0.0004	
B –CCS	384.00	1	384.00	192.00	0.0008	
AB	16.00	1	16.00	8.00	0.0663	**0.9950**
A2	40.50	1	40.50	20.25	0.0205	
B2	98.00	1	98.00	49.00	0.0060	
Cor Total	1206.00	8	-	-	-	

Table 14: Formulation of checkpoint batch F10

SR.NO	Formulation Ingredients(Mg)	Formulation Batch F10
1	Inclusion complex containing 50mg of Avanafil	100
2	Sodium starch glycolate	14.83
3	Crosscarmellose sodium	8.09
4	Microcrystalline cellulose	10
5	Aspartame	3
6	Talc	4
7	Magnesium stearate	2
8	Mannitol QS	38.08
	Total weight(mg)	180

Table 15: Evaluation Parameters of checkpoint batch F10

Precompression evaluation Parameters	
Bulk density(gm/ml)	0.286± 0.11
Tapped density(gm/ml)	0.325± 0.63
Carr's compressibility index (%)	12.5± 0.24
Hausner ratio	1.06± 0.33
Angle of repose(°)	27.42±0.03
Evaluation parameters of Tablets	
Weight variation	179 ±1.52
Hardness (kg/cm2)	3.3±0.17
Thickness (mm)	2.4±0.02
Friability (%)	0.45± 0.04
Disintegration time (sec)	21±1.000
Wetting time (sec)	27±0.577
% Drug content	99.12±1.15
Drug release (%) in 10 min	97.45±0.79

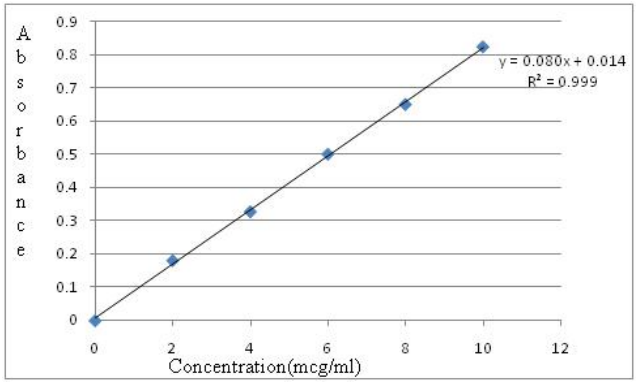

Figure 1: Calibration curve of Avanafil in 0.1 N HCl buffer pH 1.2

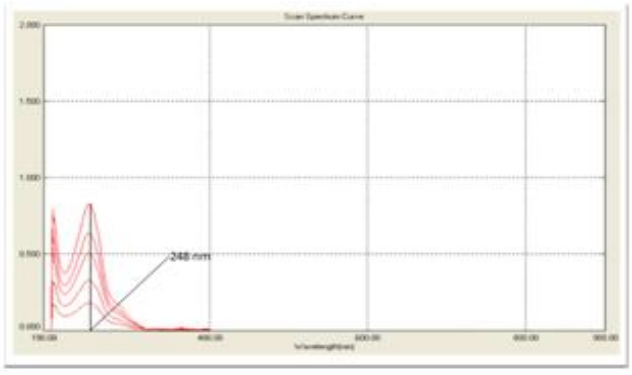

Figure 2: The overlay UV spectra of Avanafil in 0.1 N HCl buffer pH 1.2

Figure 3: FTIR Spectra of Avanafil

Drug-Excipients Compatibility Study by FT–IR

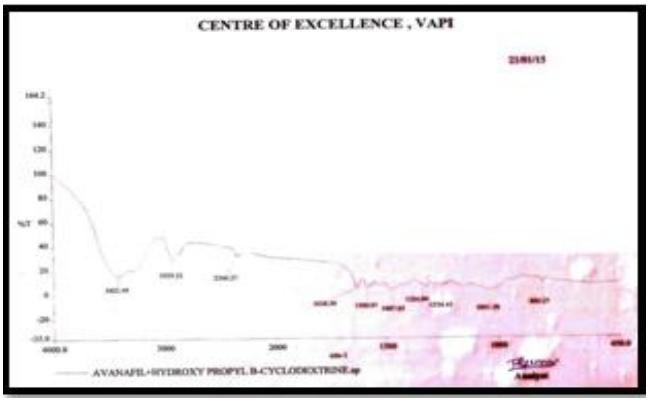

Figure 4: FTIR Spectra of Avanafil: HP-β-CD (1:1 molar ratio) inclution complex

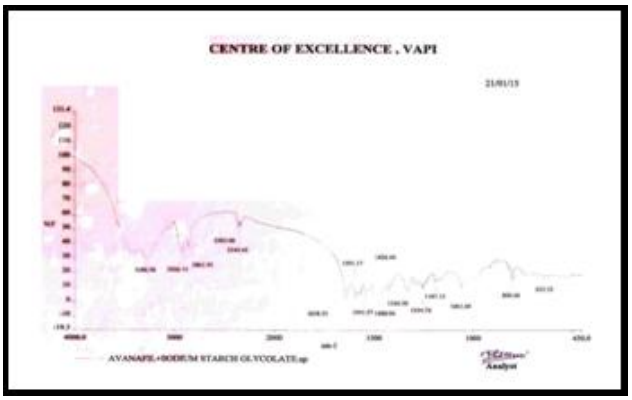

Figure 5: FTIR spectra of drug + Sodium Starch Glycolate

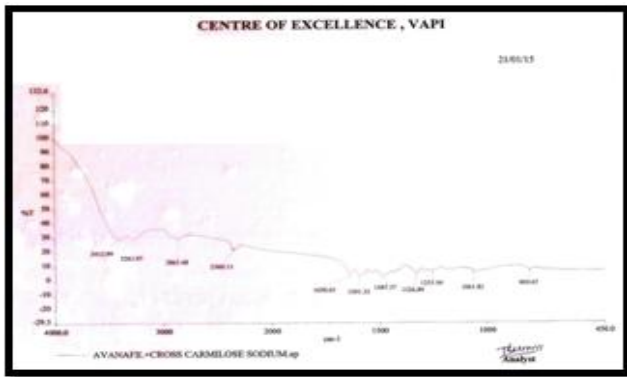

Figure 6: FTIR spectra of drug + Cross Carmellose Sodium

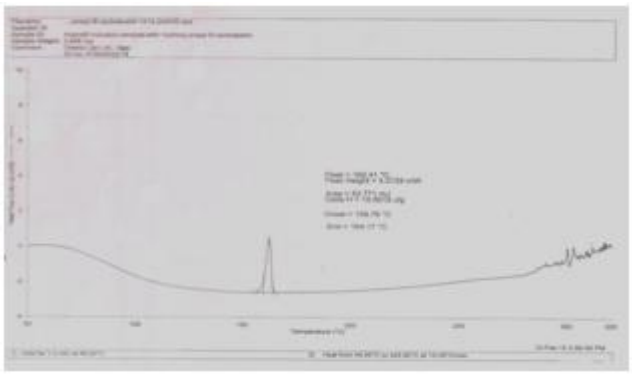

Figure 7: DSC Spectra of Avanafil and complex containing hydroxyl propyl-β- cyclodextrin

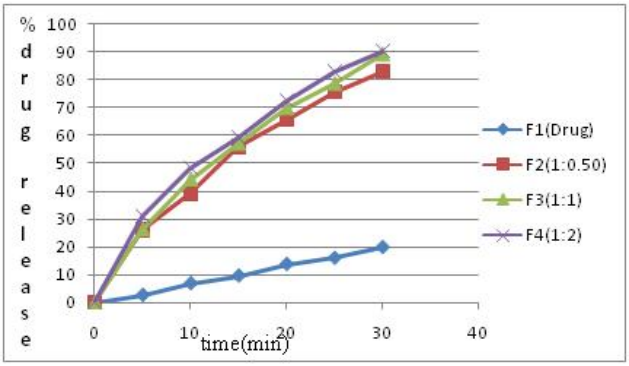

Figure 8: Comparative Dissolution Profiles of Various Molar Ratios of Avanafil Hydroxy propyl β–Cyclodextrin complex

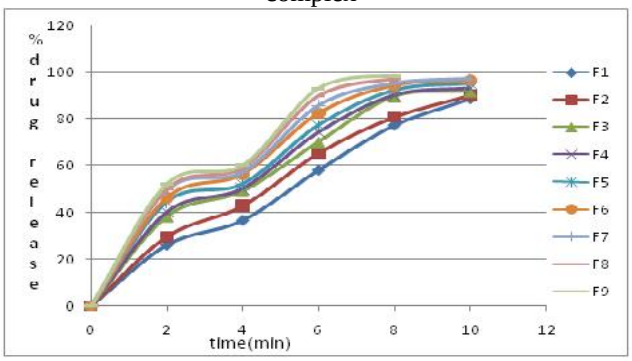

Figure 9: Effect of Super disintegrants on Dissolution Profiles of Factorial Batches (F1-F9)

Response Surface Plots

Effect of X1 and X2 on Disintegration Time

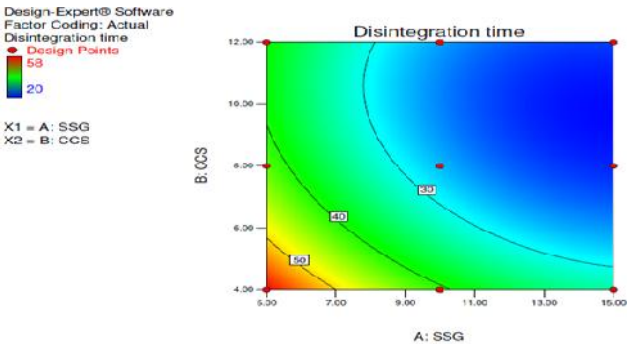

Figure 10: Two-Dimensional Contour Curve for Disintegration Time

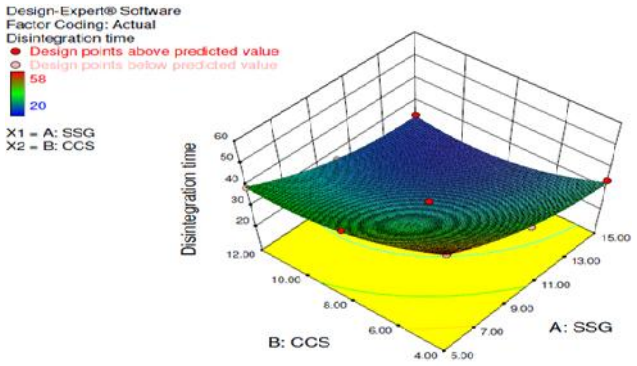

Figure 11: 3-D graph showing effect of SSG and CCS on Disintegration Time

This contour plot shows the effect of concentration of Sodium starch glycolate (X1) and concentration of Croscarmellose (X2) on disintegration time (Y1). As concentration of X1 and X2 increases, the value of response Y1 decreases.

Effect of X1 and X2 on Wetting Time

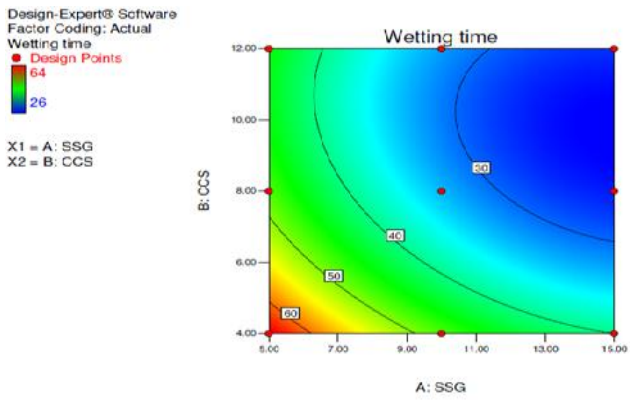

Figure 12: Two-Dimensional Contour Curve for Wetting Time

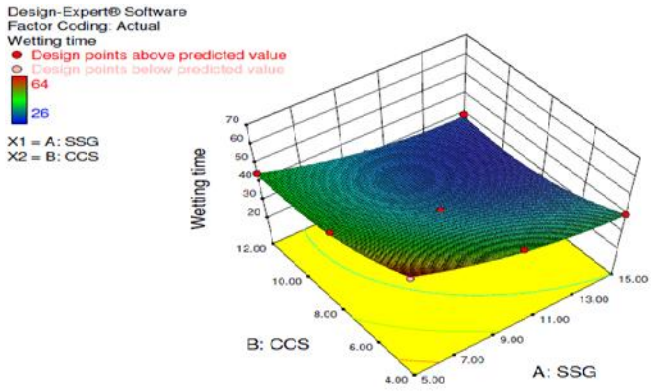

Figure 13: 3-D graph showing effect of SSG and CCS on Wetting Time.

This contour plot shows the effect of concentration of Sodium starch glycolate (X1) and concentration of Croscarmellose (X2) on wetting time (Y2). As concentration of X1 and X2 increases, the value of response Y2 decreases.

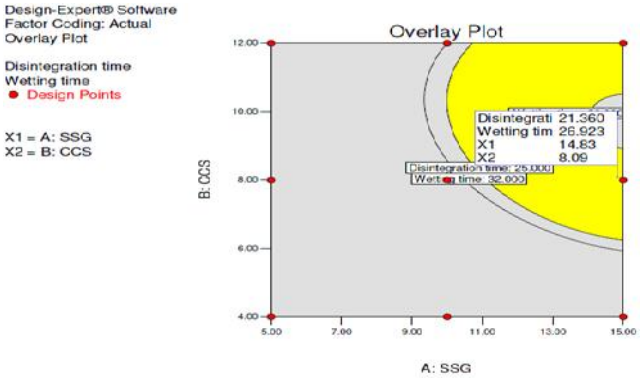

Figure 14: Overlay Plot of Response Variables

5. Acknowledgement

Authors wish to thank OM Laboratories Ahmedabad, Gujarat for providing Avanafil sample. The authors are also thankfull Vishal chem. Mumbai and Lobachemi for providing excipients. The authors are also thankfull to the principal, Smt. B.N.B Swaminarayan Pharmacy for providing all the necessary facilities required for the research work.

6. References

1. Ghosh TK, Pfister WR, "Drug delivery to the oral cavity molecules to market", U.S.A: Taylor and Francis group, **2005**, pp. 261-89.
2. Liberman HA, Lachman L, Schwartz JB. Pharmaceutical dosage forms tablet volume1; 2nd edn, New York: Marcel Dekker Inc, **2005**, pp. 75-7.
3. Bandari S, Mittapalli RK, Gannu R and Rao YM. Asian J Pharm. **2008,** 2(1):2-11.
4. Geeta Rajput and Amit Kumar.The Pharma Innovation – Journal. **2013** Vol. 2(2):144-152.
5. D Bhowmik, Chiranjib.B, Krishnakanth and Pankaj, R.Margret Chandira**.** Journal of Chemical and Pharmaceutical Research. **2009**, 1(1): 163-177.
6. Jasmin Kubawat, YK. Agrawal, Unnati S. Patel. Am. J. PharmTech Res. **2013**, 3(3): 113-120.
7. Martin A. Solubility and Distribution Phenomena. 6th edition. Lippincott Williams and Wilkins; **2011**. (Physical Pharmacy and Pharmaceutical Sciences).
8. Chordiya Mayur A and Senthilkumaran K.Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences. **2012**; 1(1):19-28.
9. Pandya SJ, Mansuri JS, Patel P. Compatible Polymer used as complexes in various drug delivery systems: β-Cyclodextrin, Pharmainfo net. **2008**; 6(2)
10. Hitendra S Mahajan, Swapnil R Bhagirath. Indian Journal of Novel Drug Deliver. **2014,** 6(1):1-9.
11. Dr. Zhen-Hai Zhang and Jian-Ping Zhou. Journal of China Pharmaceutical University Pharmazie **2012,** 67: 46–53.

12. Patil.C. African Journal of Pharmacy and Pharmacology. **2011** Vol. 5(1). pp. 76-82.
13. Takako Ishiguro, Kaneto Uekama and Hidetoshi Arima. Journal of Pharmaceutical Sciences. **2011**, Volume 100, Issue 5 Pages 1935–1943.
14. Green J. M. 1996 (May 1). A practical guide to analytical method validation, Anal Chem.News Feat 305A/309A.
15. International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human use. **1996**. Validation of Analytical procedures: Methodology.ICHQ2B, Geneva, (CPMP/ICH/281/95).
16. Lewis GA, Mathieu D, The scope of experimental design, Pharmaceutical Experimental Designs, Marcel Dekker.NewYork, **1999**; 50.
17. R. M. Franz, J. E. Browne, A. R. Lewis, Experiment design, modeling and optimization strategies for product and process development, In: H. A. Libermann, M. M.Reiger, G. S. Banker, eds. Pharmaceutical Dosage Forms: Disperse Systems, Vol 1. Marcel Dekker, New York **1988**, pp. 427-519.
18. Patel DM, Patel NM, Shah RR, Jogani PD and Balapatel AI. Indian J. Pharm. Sci. **2004**,
19. 66 (5): 621-625.
20. Changoiwala Nitu, Mehta Krupa and Modi Sanjay C. International Journal of Pharmaceutical Research and Bio-Science. **2012**; Volume 1(6): 218-238.
21. SJ. Bhyan, B.Bhupinder, G.Mohan, H.Singh. Der Pharmacia Lettre. **2013**, 5, 31-42.
22. Raymond C Rowe, Paul J Sheskey and Marian: Handbook of pharmaceutical excipients, 6nd edn. American Pharmaceutical Association, Washington.