Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(10):259-274

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Design Development & *In-Vitro* Evaluation of Oral Rapid Mouth Dissolving Tablet Containing Sildenafil Aspirin Co-Crystals Using QbD Approach

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ABSTRACT

The main objective of the present investigations was to apply quality by design (QbD) approach for the development of Oral Dispersible tablet containing Sildenafil Aspirin Co-crystals. Critical ingredients and the process parameters are linked to the critical quality attributes of the well desired product. Variability is reduced by the product and the process understanding which leads to quality improvement, risk reduction and ultimately productivity enhancement. Sildenafil citrate is a well-known selective inhibitor of phosphodiesterase type 5 enzyme (PDE5) extensively used for the treatment of erectile dysfunction (ED). Sildenafil citrate is a BCS class II drug having a low aqueous solubility so co-crystallization with Aspirin is a method of choice to increase the solubility and to have the quicker onset of action by avoiding the first pass metabolism, an oral rapid mouth dissolving tablets had been prepared using Sildenafil Aspirin co-crystals. Fast dissolving tablets of Sildenafil Aspirin Cocrystals were designed, developed, optimized and characterized by using statically 3^2 factorial design in which two variables namely the concentration of crosspovidone and the concentration of SSG were at three levels (low, medium and high). The main interactive influences were tested using the statistical model. The response surface plots were generated by the software for analyzing the effects of the independent variables on the response. All the batches of the oral dispersible tablet were prepared by the direct compression method. The tablets were evaluated for Pre-compression parameters e.g. Bulk density, Tapped density, Angle of repose, Carr's compressibility index and Hauser's ratio and also post compression parameters like hardness, wetting time, drug content uniformity, friability, Thickness, Disintegration time & In vitro dissolution. The 3^2 full factorial design revealed that the amount of super disintegrants significantly affect the dependent variables disintegration time and wetting time.

Keywords: Sildenafil aspirin co-crystals; Crosspovidone; *In-vitro* disintegration; *In-Vitro* dissolution; Oral dispersible tablet

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INTRODUCTION

Quality by design (QbD) is an intelligent systematic approach to design quality products by systematic process. The principles of QbD is best explained by ICH Q8, ICH Q9 & ICH Q10, which gives the guidance on Science & Risk-based assessment, product's life cycle and its approach, and the various method designs.

QbD principles promote innovation and continuous improvement of the product quality. Knowledge-based commercial manufacturing ensures enough regulatory flexibility for setting specifications and post-approval changes. Product and process are designed using innovative risk-based techniques to meet predefined quality objectives thereby satisfying the most critical patient needs and regulatory requirements at low cost.

Experimental Design or DOE is defined as "a structured analysis wherein the inputs are changed and differences or variations in outputs are measured to determine the magnitude of the effect of each of the inputs or combination of inputs." Factorial designs allows for the simultaneous study of the effects like concentration of super disintegrants

and concentration of diluents on the physical characteristics of the tablet. There are several advantages to statistically designed experiments, and when compared with other test methods, the results are outstanding. DOE is strongly favored by the regulatory agencies, because it justifies the choice of ranges and finds a robust (optimum) region. In addition, it gives the researcher the ability to study the interactions between factors. DOE provides a more economical use of the resources, especially when many factors exists and provides a greater chance of finding optimum conditions. Finally, predictions can be made about future experiments.

In the development of pharmaceutical dosages form with appropriate characteristics an important issue is to design an optimized pharmaceutical formulation in a short time of periods with minimum trials. For that now a day's response surface methodology (RSM) gaining attention to identify and quantify the effect of different formulation variables on the important characteristics. The aim of this study was to develop, optimize and characterize fast disintegrating tablets by statically designed by using 3^2 factorial design in which two variables namely concentration of Cross Povidon and concentration of Sodium Starch Glycolate (SSG) were at two levels. The main interactive influences were tested using statistical model. The response surface plots were generated by software for analyzing effect of the independent variables on the response. The effect of formulation variables on the product characteristics can be predicted and precisely interpret by using a 2-level factorial design and generated quadratic mathematical equation.

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed up on the tongue". Compared to alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means to administer drugs, greater flexibility in dosage. Oral dispersible table is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Companies have given these tablets various names such as orally disintegrating tablets (ODT), mouth dissolving (MD), fast melting, fast dissolving or Orodisperse. The FDT is also known as *fast melting, fast dispersing, rapid dissolve, rapid melt,* and/or *quick disintegrating tablet.* All FDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the Term *orodispersible tablet* for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel like structure, allowing easy swallowing by patients. The disintegration time for good FDTs varies from several seconds to about a minute. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics.

MATERIALS AND METHODS

The Sildenafil Aspirin co-crystals [1] were developed and optimized in the laboratory of Faculty of Pharmacy, Dharamsinh Desai University, College Road, Nadiad – 387002 Gujarat.

Table 1: Master Formula

S. No.	Materials	Uses	Source
1	Co-crystals[1]	API	Laboratory of DDU*
2	SSG	Super Disintegrant	Merck
3	Cross Povidone	Super Disintegrant	Merck
4	Cross Carmellose	Super Disintegrant	Merck
5	Aerosil	Lubricant	Merck
6	Magnesium stearate	Lubricant	SD-fine Chemicals
7	Talc	Glident	SD-fine Chemicals
8	Lactose Q.S.	Diluent	SD-fine Chemicals

Method

Fast dissolving tablets containing Sildenafil Aspirin Co-crystals [1] were prepared by direct compression method according to the formula (Shown in Table-1).

Formulation

The formulation had been optimized by trial batches.

Trial batches

Three different super disintegrant has been selected and each superdisintegrant added in 3 different percentages (low, medium, high). Total 9 batches, 3 of each super disintegrants using different percentage proportions (6%, 8%, 10%).

Where, Batch A1, A2, A3 containing SSG (Sodium Starch Glycolate), Batch B1, B2, B3 containing Cross Povidone and Batch C1, C2, C3 containing Cross Carmellose.

Table 2: Composition of Trial Batches

Ingredients*	A1	A2	A3	B1	B2	B3	C1	C2	C3
Co-crystals	400	400	400	400	400	400	400	400	400
SSG	36 (6%)	48 -8%	60 -10%	-	-	-	-	-	-
Cross Povidone	-	-	-	36 -6%	48 -8%	60 -10%	-	-	-
Cross Carmellose	-	-	-	-	-	-	36 -6%	48 -8%	60 -10%
Aerosil	18	18	18	18	18	18	18	18	18
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
Lactose Q.S.	134	122	110	134	122	110	134	122	110
Total	600	600	600	600	600	600	600	600	600

* All the quantities are in mg

EVALUATION PARAMETERS

Pre-compression parameters

Angle of repose:

The Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated by substituting the values of the base radius "R" and pile height "H" in the following equation (Aulton, 2003)

$\tan \theta = H / R$ Where,

H = Pile height and R = Radius of Pile Therefore;

$\theta = \tan^{-1} H / R$

Bulk density

The sample equivalent to 25g was accurately weighed and filled in a 100 ml graduated cylinder and the powder was leveled and the unsettled volume, Vo was noted. The bulk density was calculated by the formula (Lachman et al, 1991)

Bulk density (ρ_o) = M/V_o Where,

M = mass of powder taken, V_o = Apparent unstirred volume

Tapped density

The tapped density was determined by mechanically tapping the measuring cylinder and the volume was noted (Lachman et al, 1991)

Tapped density (ρ_t) = M / V_t Where, ρ_t = tapped density

M = weight of granules V_t = tapped volume of granules in cm^3

Compressibility index

The bulk volume and tapped volume was measured and compressibility index was calculated using the formula (Aulton, 2003).

Compressibility index =$100 (V_o-V_f)/V_o$ Where,V_o = Bulk volume V_f = Tapped volume

Hausner's ratio

Tapped volume and bulk volume were measured and the hausner"s ratio was calculated using the formula

Hausner's ratio = V_o/V_f

Where, Vo = Bulk volume Vf = Tapped volume

Table 3: Scale of Flowability

Flow Character	Carr's Index	Hausner Ratio	Angle of Repose [ɵ]
Excellent	≤ 10	1.0-1.11	25 – 30
Good	15-Nov	1.12 – 1.18	31 - 35
Fair	16 - 20	1.19 – 1.25	36 - 40
Passable	21 - 25	1.26 – 1.34	41 - 45
Poor	26 - 31	1.35 – 1.45	46 - 55
Very Poor	32 - 37	1.45 – 1.59	56 - 65
Very, very Poor	>38	> 1.60	> 66

Pre-compression parameter study

The tablet blends were evaluated for their bulk density, tapped density, carr's index and flow properties.

Table 4: Results of Pre formulation studies of Trial batches

Preformulation Parameters	A1	A2	A3	B1	B2	B3	C1	C2	C3
Bulk density	0.59	0.57	0.58	0.59	0.58	0.58	0.59	0.57	0.57
Tapped density	0.72	0.73	0.7	0.69	0.72	0.68	0.7	0.71	0.73
Angle of repose	32	32	31	31	32	33	31	32	32
% Compressibility	18.06	21.92	17.14	14.49	19.44	14.71	15.71	19.72	21.92
Hausner's ratio	1.22	1.28	1.21	1.17	1.24	1.17	1.19	1.25	1.28

* A= SSG, B= Cross Povidone, C= Cross Carmellose

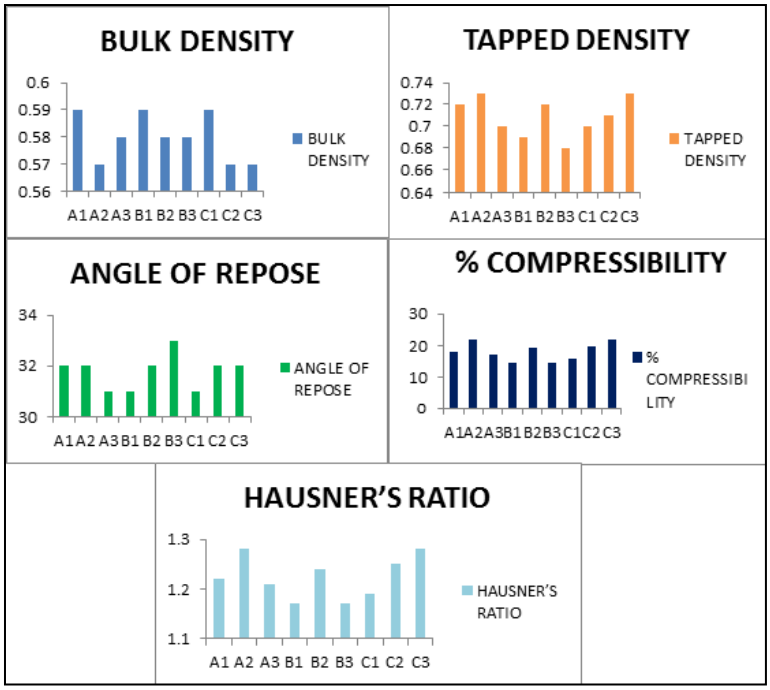


Figure 1: Graphical representation of the results of Pre formulation studies of Trial batches

The trial batches containing cross povidone as super disintegrant shows good compressibility.

Post formulation result of Trial Batches (A1, A2, A3, B1, B2, B3, C1, C2, C3) tablet evaluation

The tablets of the Trial 3 batches containing single super disintegrant at three different percentage level has been undergone post formulation studies and the results have been reported under below table.

Table 5: Results of Post formulation studies of trial batches

Parameters	A1	A2	A3	B1	B2	B3	C1	C2	C3
Disintegration time (sec)	91	78	72	40	35	30	181	169	150
Hardness (Kg/cm^2)	3.5	3.2	3	3.5	3.6	3.4	3.5	3.7	3.8
Friability (%)	0.67	0.67	0.67	0.6	0.58	0.59	0.57	0.55	0.54
Wetting time (Sec.)	67± 1	62±1	58 ± 1	53± 1	47± 1	40± 1	91± 1	95± 1	91± 1

*A= SSG, B= Cross Povidone, C= Cross Carmellose

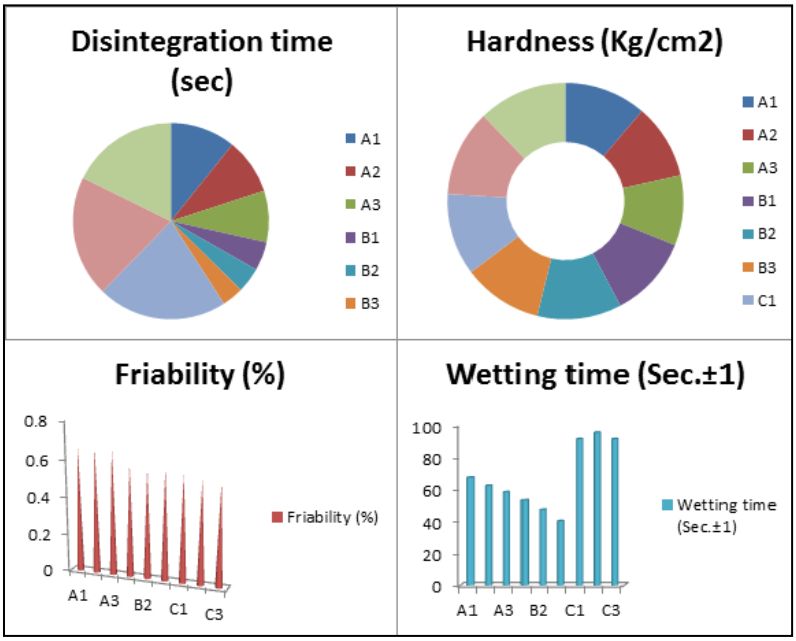


Figure 2: Graphical representation of the results of post formulation studies of Trial batches

Optimization by factorial design

On reviewing the preliminary trial results, combination of two super disintegrants with different percentage of concentration (5%, 7.5%, 10%) has been selected and design 3^2 matrix i.e 2 factors evaluated at 3 levels (from Design expert software (version 7.02) .

Table 6: Optimization by factorial design

2 FACTORS (Independent variable)		
Cross Povidone (X1) (Super Disintegrants)		**SSG (X2)** (Super Disintegrants)
2 Variables (Dependent)		
Dis-integration time (Y1)		**Wetting time (Y2)**
3 LEVELS		
Low	**Medium**	**High**
-1	0	+1
(5%)	(7.5%)	(10%)

As per the design expert software there were 9 batches designed

Table 7: Levels of two Super Disintegrants for the 9 factorial designed batches

9 BATCHES AS PER FACTORIAL DESIGN									
Cross Povidone (X1)	-1	-1	-1	0	0	0	1	1	1
SSG (X2)	-1	0	1	-1	0	1	-1	0	1

Table 8: Amount in % of two Super Disintegrants for the 9 factorial designed batches

FACTORIAL BATCH DESIGN									
Batch	A1	A2	A3	A4	A5	A6	A7	A8	A9
Cross Povidone (X1)	0.50%	0.50%	0.50%	7.50%	7.50%	7.50%	10%	10%	10%
SSG (X2)	0.50%	7.50%	10%	0.50%	7.50%	10%	0.50%	7.50%	10%

Table 9: Batches of Formulation as per Factorial Design

Sr. No.	Material	A1	A2	A3	A4	A5	A6	A7	A8	A9
1	Co-crystals	400	400	400	400	400	400	400	400	400
2	SSG	30	45	60	30	45	60	30	45	60
3	Cross Povidone	30	30	30	45	45	45	60	60	60
4	Aerosil	18	18	18	18	18	18	18	18	18
5	Magnesium stearate	6	6	6	6	6	6	6	6	6
6	Talc	6	6	6	6	6	6	6	6	6
7	Lactose Q.S.	110	105	90	105	80	65	90	65	50
8	Total	600	600	600	600	600	600	600	600	600

Pre-formulation – Factorial Design Batches (A1, A2, A3, A4, A5, A6, A7, A8, A9) Powder blend evaluation

Table 10: Results of Pre formulation studies of factorial designed batches

Preformulation Parameters	A1	A2	A3	A4	A5	A6	A7	A8	A9
Bulk density	0.57	0.59	0.58	0.56	0.59	0.57	0.58	0.59	0.58
Tapped density	0.7	0.68	0.65	0.72	0.69	0.7	0.72	0.76	0.65
Angle of repose	32	32	30	33	31	32	32	30	31
% Compressibility	18.6	13.2	10.8	22.2	14.5	18.6	19.4	22.4	10.8
Hausner's ratio	1.23	1.15	1.12	1.29	1.17	1.23	1.24	1.29	1.12

A1-A9 = Containing diff. proportions of SSG + Cross Povidone

All the ingredients were passed through 60 # sieve separately, Magnesium stearate & Talc through 40 #. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed flat round punch to get tablet using tablet Compression Machine.

Table 11: Pre-compression parameter study result

S. No.	Formulation code	Angle of repose	Bulk density	Taped density	Hausner ratio	% Compressibiliy
1	A1	32	0.57	0.7	1.23	18.6
2	A2	32	0.59	0.68	115	13.2
3	A3	30	0.58	0.65	1.12	10.8
4	A4	33	0.56	0.72	1.29	22.2
5	A5	31	0.59	0.69	1.17	14.5
6	A6	32	0.57	0.7	1.23	18.6
7	A7	32	0.58	0.72	1.24	19.4
8	A8	30	0.59	0.76	1.29	22.4
9	A9	31	0.58	0.65	1.12	10.8

Post compression parameter study Average weight and weight variation: For weight variation test IP procedure was followed. Twenty tablets were taken and their weight was determined individually and collectively using single pan electronic balance (AR 0640, Ohaus Corp. USA). The average weight of the tablets was determined from collective weight. From the individual tablets weight, the range and percentage standard deviation was calculated. Not more than 2 tablets should deviate from the average weight of tablets and the maximum percentage of deviation allowed.

In direct compression of tablet, uniform weight of tablets represents appropriate powder flow and uniform die filling.

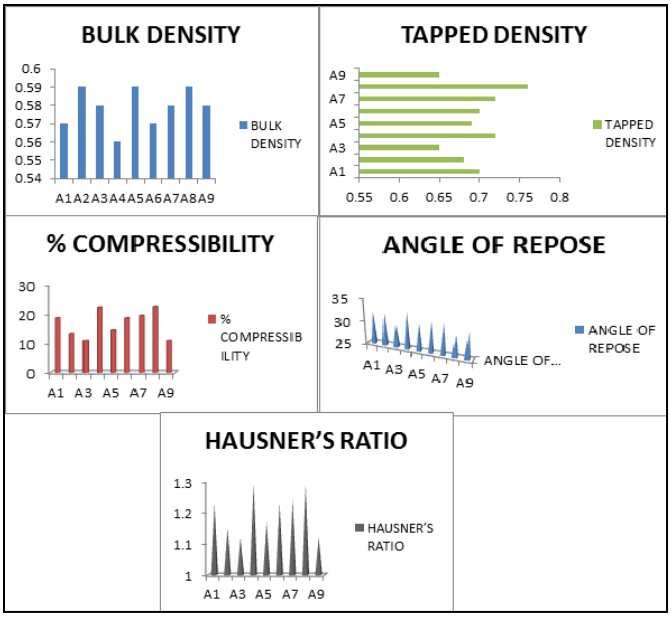


Figure 3: Graphical representation of the results of Pre formulation studies of factorial designed batches

Hardness

Hardness exhibits tensile strength of tablet. The force needed to fracture the tablet by diametral compression is referred as crushing strength of tablet. Hardness is a deformation property of a solid. The hardness of the six tablets from each formulation batch was determined using Monsanto hardness tester.

Friability

Friability test indicates physical strength of compressed tablets. During handling tablets are subjected to stresses from collisions and tablets sliding towards one another and other solid surfaces, which can result in the removal of small fragments and particles from tablet surface. The result will be progressive reduction in tablet weight and a change in its appearance. Test for tablet Friability was carried out according to I.P 2007, according to which friability below 1% passes the test. Tablets from each formulation were tested for friability using Roche Friabilator (Rolex Scientific Engineers Limited). Twenty tablets were weighed initially and transferred to the Friabilator. The instrument was operated at 25 rpm for 4 minutes. The tablets were reweighed and percentage loss was calculated using formula:

Post formulation – Factorial Design Batches (A1, A2, A3, A4, A5, A6, A7, A8, A9) tablet evaluation

Table 12: Results of Post formulation studies of factorial designed batches

Parameters	A1	A2	A3	A4	A5	A6	A7	A8	A9
Disintegration time (sec)	52	48	46	43	41	38	35	32	29
Hardness (Kg/cm^2)	3.6	3.5	3.4	3.4	3.2	3.2	3	3	3.2
Friability (%)	0.68	0.65	0.64	0.64	0.6	0.62	0.65	0.63	0.63
Wetting time (Sec.)	65	57	56	55	52	49	48	45	40
Thickness(mm)	5.12	5	4.85	4.62	4.85	4.46	4.23	4.1	4.25

A1-A9 = Containing diff. proportions of SSG + Cross Povidone

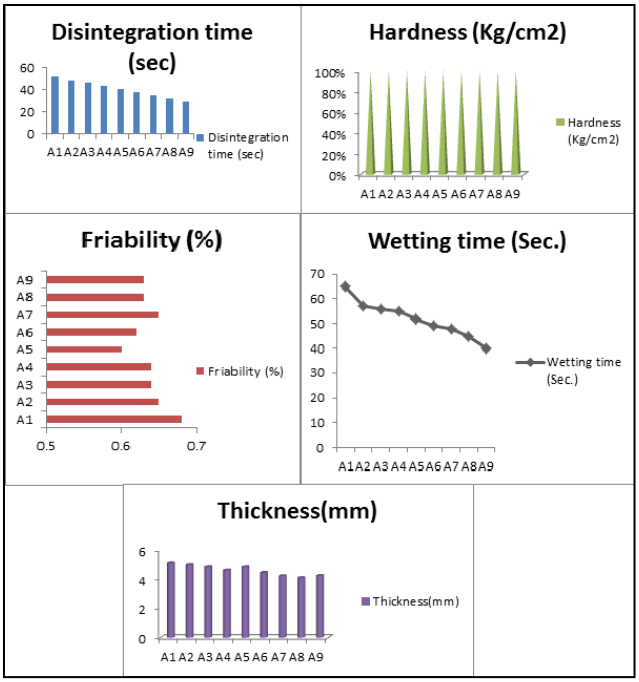


Figure 4: Graphical representation of the results of post formulation studies of factorial designed batches

Drug content (% Assay)

Validation of factorial design

The amount of the two super disintegrant has been defined by design of experiment at 3 levels i.e. -1, 0, +1 i.e. low, medium, higher level; i.e 5%, 7.5%, 10% of the total weight of tablet. From the results of the factorial designed 9 batches, the software providing 3 different level points from the designed space, to validated the designed range system whether correct or not. The coded values given by the software are defined in the below table.

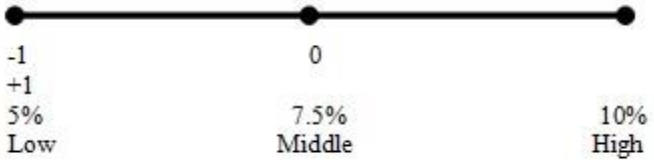
Table 13: Drug Content of factorial designed batches

Batch	Label claim (mg)		Amount found (mg)		% Label claim (mg)	
	SIL	ASP	SIL	ASP	SIL	ASP
A1	50	150	50.12	149.73	100.2	99.8
A2	50	150	50	149.6	100	99.7
A3	50	150	50.06	149.91	100.1	99.9
A4	50	150	50.03	149.87	100.1	99.9
A5	50	150	50.11	149.98	100.2	100
A6	50	150	49.98	150	100	100
A7	50	150	49.99	150.2	100	100.1
A8	50	150	50.15	149.98	100.3	100
A9	50	150	50.12	151.01	100.2	100.7

Table 14: Coded values for Level of two Super Disintegrants for the defined for 3 Coded batches for validation

Code	X1- CROSS POVIDONE	X2-SSG
C1	0.25	-0.85
C2	0.56	-0.66
C3	0.14	0.54

Calculation



If coded value is 0.25, then calculate it as 0 is middle value 7.5 % so 0.25 is 8.125%

Table 15: Amount in % for Level of two Super Disintegrants for the defined for 3 Coded batches for validation

Code	X1- CROSS POVIDONE	X2-SSG
C1	8.13%	5.38%
C2	8.75%	5.85%
C3	7.85%	8.85%

Table 16: Composition for 3 Coded batches for validation

Ingredients*	C1	C2	C3
Co-crystal	400	400	400
SSG	32.25	35.1	53.1
Cross Povidone	48.75	52.5	47.1
Aerosil	18	18	18
Talc	6	6	6
Magnesium Sterate	6	6	6
Mannitol Q.S.	89	82.4	69.8
Total	600	600	600

* All the quantities are in mg.

Post formulation – factorial design batches (A1, A2, A3, A4, A5, A6, A7, A8, A9) tablet evaluation

Table 17: Results of Post formulation studies of factorial designed batches

Parameters	A1	A2	A3	A4	A5	A6	A7	A8	A9
Disintegration time (sec)	52	48	46	43	41	38	35	32	29
Hardness (Kg/cm^2)	3.6	3.5	3.4	3.4	3.2	3.2	3	3	3.2
Friability (%)	0.68	0.65	0.64	0.64	0.6	0.62	0.65	0.63	0.63
Wetting time (Sec.)	65	57	56	55	52	49	48	45	40
Thickness(mm)	5.12	5	4.85	4.62	4.85	4.46	4.23	4.1	4.25

A1-A9 = Containing diff. proportions of SSG + Cross Povidone

Drug Content (% Assay)

Table 18: Drug Content of factorial designed batches

Batch	Label claim (mg)		Amount found (mg)		% Label claim (mg)	
	SIL	ASP	SIL	ASP	SIL	ASP
A1	50	150	50.12	149.73	100.2	99.8
A2	50	150	50	149.6	100	99.7
A3	50	150	50.06	149.91	100.1	99.9
A4	50	150	50.03	149.87	100.1	99.9
A5	50	150	50.11	149.98	100.2	100
A6	50	150	49.98	150	100	100
A7	50	150	49.99	150.2	100	100.1
A8	50	150	50.15	149.98	100.3	100
A9	50	150	50.12	151.01	100.2	100.7

Evaluation of the dissolution study of factorial designed 9 batches (A1, A2, A3, A4, A5, A6, A7, A8, A9)

Dissolution study has been carried out for the factorial designed batches and the samples have been withdrawn at 2, 4, 6, 8, 10, 12 and 14 minutes. The samples were filtered and scan under UV spectrophotometer and the spectra has been converted to first order derivative and then the absorbance has been measured at two wavelengths i.e. at 255 nm for Sildenafil citrate (at ZCP of Aspirin) and at 291 nm for Aspirin (at ZCP of Sildenafil Citrate).

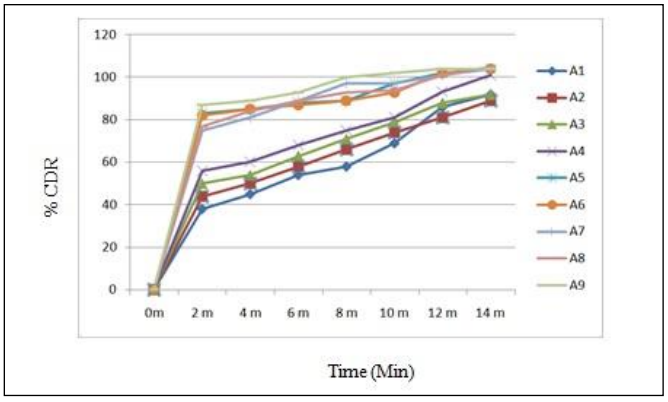


Figure 5: Graphical representation of the % Cumulative Drug Release vs. Time of A1-A9 batches

Effect on disintegration time- response surface plot

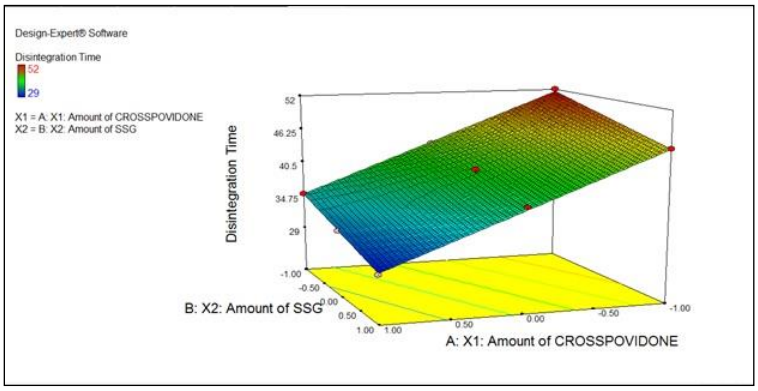


Figure 6: Effect on Disintegration Time- Response Surface Plot

Effect on disintegration time - contour plot

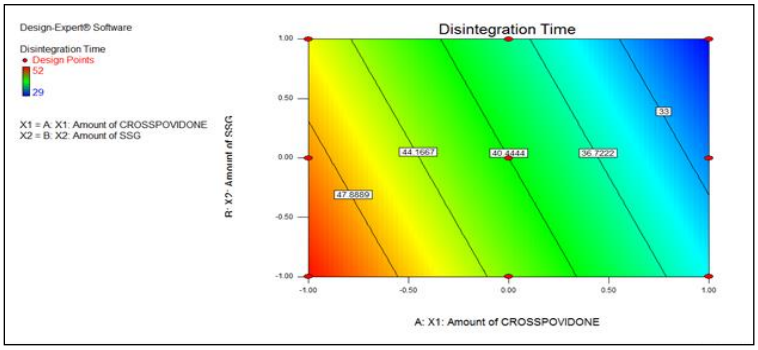


Figure 7: Effect on Disintegration Time- Contour Plot

ANOVA – effect on disintegration time

Table 19: ANOVA – Effect on Disintegration Time

Source	Sum of Square	df	Mean Square	F value	p-value Prob > F
Model Significant	464.83	2	232.42	1004.04	<0.0001
A-X1	416.67	1	416.67	1800	<0.0001
B-X2	48.17	1	48.17	208.08	<0.0001
Residual	1.39	6	0.23		
Cor Total	466.22	8			

A-X1: Amount of CROSSPOVIDONE
B-X2: Amount of SSG

The Model F-value of 1004.04 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Table 20: Summary ANOVA

Std. Dev.	0.48	R-Squared	0.997
Mean	40.44	Adj R-Squared	0.996
C.V. %	1.19	Pred R-Squared	0.9941
PRESS	2.77	Adeq Precision	80.4

The "Pred R-Squared" of 0.9941 is in reasonable agreement with the "Adj R-Squared" of 0.9960. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 80.400 indicates an adequate signal. This model can be used to navigate the design space.

Table 21

Factor	Coefficient estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	40.44	1	0.16	40.05	40.84	
A-X1	-8.33	1	0.2	-8.81	-7.85	1
B-X2	-2.83	1	0.2	-3.31	-2.35	1

A-X1: Amount of CROSSPOVIDONE
B-X2: Amount of SSG

Final Equation in Terms of Coded Factors: Disintegration Time (Y1) = +40.44 -8.33 * A -2.83 * B
Final Equation in Terms of Actual Factors: Disintegration Time (Y1) = +40.44444 -8.33333 * X1: Amt of CP -2.83333 * X2: Amount of SSG

Effect on wetting time - response surface plot

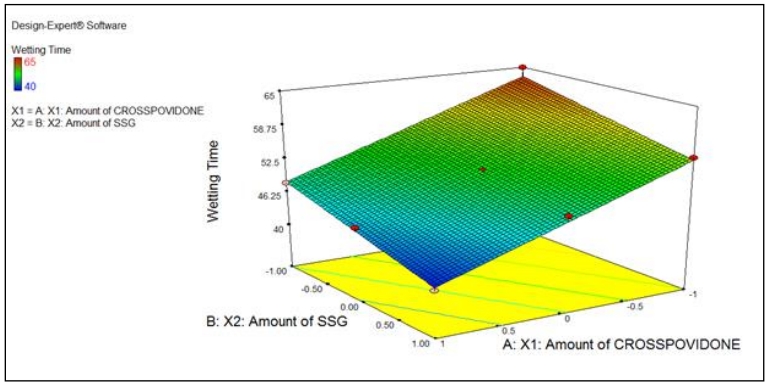


Figure 8: Effect on Wetting Time - Response Surface Plot

Effect on wetting time - contour plot

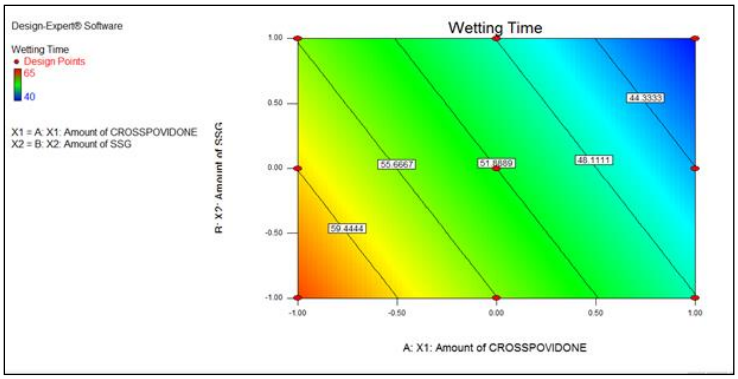


Figure 9: Effect on Wetting Time - Contour Plot

ANOVA - effect on wetting time

Table 22: ANOVA - Effect on Wetting Time

Source	Sum of Square	df	Mean Square	F value	p-value Prob > F
Model Significant	425.67	2	212.83	113.79	< 0.0001
A-X1	337.5	1	337.5	180.45	< 0.0001
B-X2	88.17	1	88.17	47.14	0.0005
Residual	11.22	6	1.87		
Cor Total	436.89	8			

A-X1: Amount of CROSSPOVIDONE
B-X2: Amount of SSG

The Model F-value of 113.79 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case A, B are significant model terms.

Table 23

Std. Dev.	1.37	R-Squared	0.9743
Mean	51.89	Adj R-Squared	0.9658
C.V. %	2.64	Pred R-Squared	0.9395
PRESS	26.42	Adeq Precision	28.707

The "Pred R-Squared" of 0.9395 is in reasonable agreement with the "Adj R-Squared" of 0.9658. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable.The ratio of 28.707 indicates an adequate signal. This model can be used to navigate the design space.

Table 24

Factor	Coefficient estimate	df	StandardError	95% CI Low	95% CI High	VIF
Intercept	51.89	1	0.46	50.77	53	
A-X1	-7.5	1	0.56	-8.87	-6.13	1
B-X2	-3.83	1	0.56	-5.2	-2.47	1

A-X1: Amount of CROSSPOVIDONE
B-X2: Amount of SSG

Final Equation in Terms of Coded Factors: Wetting Time (Y2) = +51.89 - 7.50 * A - 3.83 * B
Final Equation in Terms of Actual Factors: Wetting Time (Y2) =+ 51.88889 -7.50000 * X1: Amt of Cross Povidone -3.83333 * X2: Amt of SSG

Table 25: Summary of the evaluation by Design of Experiment

Name	Goal	Lower Limit	Upper Limit	Lower weight	Upper weight	Importance
X1	In range	-1	1	1	1	3
X2	In range	-1	1	1	1	3
DT (Y1)	Minimize	29	52	1	1	3
WT(Y2)	Minimize	40	65	1	1	3

Where, X1: Amount of CROSSPOVIDONE; X2: Amount of SSG; Y1: Effect on Disintegration Time; Y2:Effect on Wetting Time

Desirability

Table 26: Desirability

Sr. No.	X1	X2	DT (Y1)	WT(Y2)	Desirability
1	1	1	29.27	40.55	0.983

The desirability shows 0.983 which is considerable very good for +1 +1 level of both X1 & X2 batch i.e. Batch A9.

Evaluation of the Validation Batches of the Factorial Design

Table 27: Results of the Validation Batches

Code	DISINTEGRATION TIME Y1 (Sec.)		WETTING TIME Y2 (Sec.)	
	Predicted Value	Actual Result	Predicted Value	Actual Result
C1	42.45	42	29.62	29
C2	48.99	48	36.13	36
C3	49.99	49	40.87	40

From the point 5.3.13 and 5.3.17 equations, when put the values of the amount selected at random from the design space given by the software for coded batches, we can calculate the predicted values for the validation batches. The actual results are also shown in the table in comparison with the predicted values. The result shows no significant difference in Variables Y1 (Disintegration time) and Y2 (Wetting Time). So it is concluded that the designed space has been validated.

Statistical Comparison of the Predicted Results and Actual Results of the Coded Batches for Disintegration Time and Wetting Time

Table 28: Paired T-test Disintegration Time

DISINTEGRATION TIME Y1 (Sec.)		
Coded batches	Predicted Value	Actual Result
C1	42.45	42
C2	48.99	48
C3	49.99	49

t-Test: Paired Two Sample for Means		
	Variable 1	*Variable 2*
Mean	47.143333	46.33333
Variance	16.770533	14.33333
Observations	3	3
Pearson Correlation	0.9999495	
Hypothesized Mean Difference	0	
df	2	
t Stat	4.5	
P(T<=t) one-tail	0.023001	
t Critical one-tail	2.9199856	
P(T<=t) two-tail	0.0460019	

t Critical two-tail	4.3026527	

Table 29: Paired T-test Wetting Time

WETTING TIME Y2 (Sec.)		
Coded batches	**Predicted Value**	**Actual Result**
C1	29.62	29
C2	36.13	36
C3	40.87	40

t-Test: Paired Two Sample for Means		
	Variable 1	Variable 2
Mean	35.54	35
Variance	31.9017	31
Observations	3	3
Pearson Correlation	0.9978498	
Hypothesized Mean Difference	0	
df	2	
t Stat	2.4846743	
P(T<=t) one-tail	0.0654571	
t Critical one-tail	2.9199856	
P(T<=t) two-tail	0.1309143	
t Critical two-tail	4.3026527	

DISCUSSION

Pre-formulation study

In the pre-formulation study the bulk containing sildenafil Aspirin Cocrystals[1] was characterized for bulk, tapped density and angle of repose. Results of the compressibility index, Hauser's ratio and angle of repose show that the all material has sufficient compressibility and flow properties.

Selection of tabletting methodology

Formulation of mouth dissolving tablets was carried out by direct compression technique. Super disintegration addition method exhibits the lowest disintegration time. .

Trials of the mouth dissolving tablets containing of Sildenafil Asirin cocrystals [1] having various super disintegrants

SSG, Crospovidone, Cross carmellose were tried for formulation of mouth dissolving tablets. The concentration of superdisintegrants was taken 5%, 7.5% & 10%. The Powder blend was evaluated for angle of repose, Hausner's ratio and % Compressibility. The prepared tablet was evaluated for physical parameter, Wetting time, *In vitro* disintegration time, Assay and *In vitro* drug release.

Evaluation of powder blend

Angle of repose (ɵ): The angle of repose for the entire formulations blend was found to be in the range 30^o to 33^o. Formulations with crospovidone and SSG as a disintegrants showed angle of repose values < 30^o only fair flow property of the powder blend.

Compressibility index: Compressibility index was found to be in the range 10.8 % to 22.4 %. All formulations showed Fair Passable properties.

Hausner's ratio: Hausner's ratio was found to be in the range 1.12 to 1.29 and that indicated that all formulation has good flow properties.

Physical parameters

Weight variation: All the formulated (A1 to A9) tablets were passed weight variation test as the % weight variation was within the IP limits of ± 7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The prepared formulation complies with the weight variation test.

Thickness: The maximum thickness of the formulation was found to be 5.12 mm. The minimum thickness of the formulation was found to be 4.10mm. The average thickness of the all formulation was found to be 4.61mm.

Hardness: The hardness of the tablet was found to be 3.0 to 3.6 Kg/cm2.

Friability test: The maximum friability of the formulation was found to be 0.68%. The minimum friability of the formulation was found to be 0.60%. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Drug content: The drug content for the all formulation was found to be 100.2 % (max.) and 100 % (min.) for Sildenafil Citrate & 100.7% (max.) and 99.7 (min.) for Aspirin. The results were within the limit specified by the IP.

***In vitro* disintegration test:** *In vitro* Disintegration time was found to be in the range 52 to 29 sec. From all formulations, A9 has minimum disintegration time.

Wetting time: Wetting Time was found to be in the range 40 to 65 sec. From all formulations, batch A9 (10% crospovidone & 10 % SSG) has minimum wetting time.

***In vitro* drug release:** All the 9 formulations were subjected to *In vitro* dissolution studies by using Artificial Salivary fluid. Dissolution data shows that formulation A9 shows improved dissolution as compared to other formulations and total drug release was found at 10 min having 10 % crospovidone & 10 % SSG.

Comparison of formulated tablet with marketed tablet

In vitro dissolution study was carried out for conventional marketed tablet (Suhagra 50 mg, Cipla Ltd.) and compared with best formulation A9 (10 % crospovidone & 10 % SSG.). A9 had taken 10 minutes for complete drug release whereas Suhagra taken 50 minutes for complete drug release.

CONCLUSION

In the present work, mouth dissolving tablets were prepared by super disintegrant addition technique and evaluated for disintegration time, hardness and friability. The tablets were prepared using Crospovidone and SSG at different concentration. A total 9 formulations were prepared and evaluated for weight variation, thickness, friability, hardness, disintegration time, wetting time, assay and In-vitro dissolution study. The results of all formulations for Weight variation, Friability, Hardness and Assay were found to be within the IP limit and no significant variation. The Disintegration time for all formulations was found to be between 29 to 52 seconds and wetting time was between 40 to 65 seconds. Based on the In-vitro dissolution studies, it was found that the drug release for all the formulations were within 14 minutes. Formulation A9 containing Crosspovidone & SSG of each concentration 10% in concentration showed minimum disintegration time, wetting time as compare to other formulations. Dissolution studies conclude that the total drug was released within 10 minutes. The results show that disintegration time increased with the type of superdisintegrant. Crosspovidone < SSG. It was concluded that the mouth dissolving tablet of sildenafil can be formulated by superdisintegrant addition technique using crosspovidone & SSG in different concentrations.

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