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Formulation and Evaluation of Effervescent Tablet of Sildenafil Citrate and Aspirin in Combination

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ABSTRACT

The study was undertaken with an aim to formulate effervescent tablet of sildenafil citrate and aspirin in combination to achieve the immediate release and fast action of sildenafil citrate on the body with shorter period of the time and to overcome the side effect of the sildenafil citrate by simultaneous release of aspirin. A 3^2 full factorial design was applied and it revealed that the bicarbonate source (X_1) and concentration of binder (X_2) significantly affected the independent variables effervescence time (Y_1) and hardness (Y_2). The optimized formulation having citric acid 23.65 %, tartric acid 6.30 %, sodium bicarbonate 37.85 %, potassium bicarbonate 12.61 % with binder concentration 2% and hardness adjusted to 3 kg/cm^2. From among the 9 batches (D_1 – D_9) the D_3 batch have desirable property, less effervescence time, enough hardness and immediate release profile.

Keywords: Sildenafil Citrate, Aspirine, Effervecence Tablet

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INTRODUCTION

Effervescence has proved its utility as an oral delivery system in the pharmaceutical and dietary industries for decades. The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus onset of action is prolong. This can be overcome by administrating the drug in liquid from but, many APIs have limited level of stability in liquid form[1]. As per revised definition proposed to USFDA, Effervescent tablet is a tablet intended to be dissolved or dispersed in water before administration. The advantages of effervescent tablets compared with other oral dosage forms includes an opportunity for formulator to improve taste, a more gentle action on patient's stomach and marketing aspects[2]. Sildenafil citrate is phosphodiesteras type 5 (PDE5) inhibitor, used in the management of Erectile Dysfunction (ED) therapy and Pulmonary Arterial Hypertension (PAH). It has low bioavailability so with help of this effervescent formulation may leads to improve in bioavailability. Aspirin also known as acetylsalicylic acid is a salicylate drug, often used as an analgesic to relieve aches and pains and it is used to overcome the major side effect of the Sildenafil Citrate (headache). Effervescent tablets provide good patient palatability, good stomach and intestinal tolerance, improved portability, consistent response and accurate dosing.

MATERIALS AND METHOD

Sildenafil Citrate and Aspirin were obtained as gift sample from Srivalli Organics, Hyderabad and Corel pharma, Ahmedabad respectively. Citric acid anhydrous, Tartaric acid anhydrous, Sodium carbonate, Sodium bicarbonate, Magnesium bicarbonate, Potassium bicarbonate PVP K30 were purchased Finar chemicals limited, Ahmedabad. Sucralose and flavouring agents from Himedia labs, Mumbai. Weigh the Citric acid, Tartaric acid were blended and passed through Sieve No.# 40. The organic solvent was mixed with acid portions. The obtained wet mass passed through sieve no.# 20 & kept against room dryer until dry. It is called acid granulation. In base granulation firstly the sodium bicarbonate, sodium carbonate, Sildenafil Citrate and Aspirin were blended and passed through sieve no.# 40.The binding agent PVP K_{30} was dissolved in iso-propyl alcohol. The above organic solvent was mixed with base portions i.e. sodium bicarbonate & sodium carbonate. The obtained wet mass passed through sieve no. # 20 and kept against room temperature until dry. After mixing of both granules sweetener, anti foaming agent and the mixture is then added with magnesium stearate and talc to improve flow properties. The lubricated granules were compressed in rotary compression machine.

Three levels and two factors (3^2) Full Factorial Design

On the basis of the preliminary trials in the present study a 3^2 full factorial design was employed

to study the effect of independent variables, i.e X_1 and X_2. A statistical model (equation below) incorporating interactive and polynomial terms was utilized to evaluate the responses.

Table 1: Factorial Design Layout

Dependent Variables		Independent Variables	
X1	**X2**	**Y1**	**Y2**
Bicarbonate Source (mg)	Conc. Of Binder (mg)	Effervescence Time (second)	Hardness (kg/cm^2)

Table 2: Preparation of Effervescent Tablet Using 3^2 Full Factorial Design

Ingredients(mg)	D_1	D_2	D_3	D_4	D5	D6	D7	D8	D9
Sildenafil Citrate	100	100	100	100	100	100	100	100	100
Aspirin	300	300	300	300	300	300	300	300	300
Citric acid	750	750	750	750	750	750	750	750	750
Tartaric acid	322	272	200	322	272	200	322	272	200
Sodium bicarbonate	1200	1200	1200	1200	1200	1200	1200	1200	1200
Pot. bicarbonate	300	350	400	300	350	400	300	350	400
PVP K_{30}	61	61	61	68	68	68	76	76	76
Sucralose	49	49	49	49	49	49	49	49	49
Simethicone	20	20	20	20	20	20	20	20	20
Flavour (Orange)	35	35	35	35	35	35	35	35	35
Talc	22	22	22	22	22	22	22	22	22
Magnesium stearate	18	18	18	18	18	18	18	18	18
Effervescence Time	**69**	**68**	**66**	**77**	**73**	**70**	**97**	**93**	**89**
Total	**3170**	**3170**	**3170**	**3170**	**3170**	**3170**	**3170**	**3170**	**3170**

3^2 full factorial design will applied on one of best preliminary batch and after preparing all the 9 batch of factorial design the powder blend evaluated and then after the compressed tablets of D_1 to D_9 batch were evaluated.

RESULTS AND DISCUSSIONS

Drug-Excipients Compatibility Study

DSC Study

Samples were placed in pierced aluminium pans and hold for 1 min at 50 ^oC and the heated gradually at 10 ^oC min^{-1} from 50 ^oC to 300 ^oC. The onset of melting point were calculated by the instrument. DSC curves obtained for pure Sildenafil Citrate and Aspirin, and physical powder mixture of drug + excepients are shown in figure respectively. Pure powder Sildenafil Citrate showed a melting endotherm at 195.4 ^oC and Aspirin showed a melting endotherm at 143.85 ^oC.

FTIR Study

FT-IR studies were carried out for pure drug alone and along with excipients. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400 cm^{-1}. The FTIR spectra of Sildenafil Citrate, aspirin and physical mixture of the formulation components are shown in figures

below:

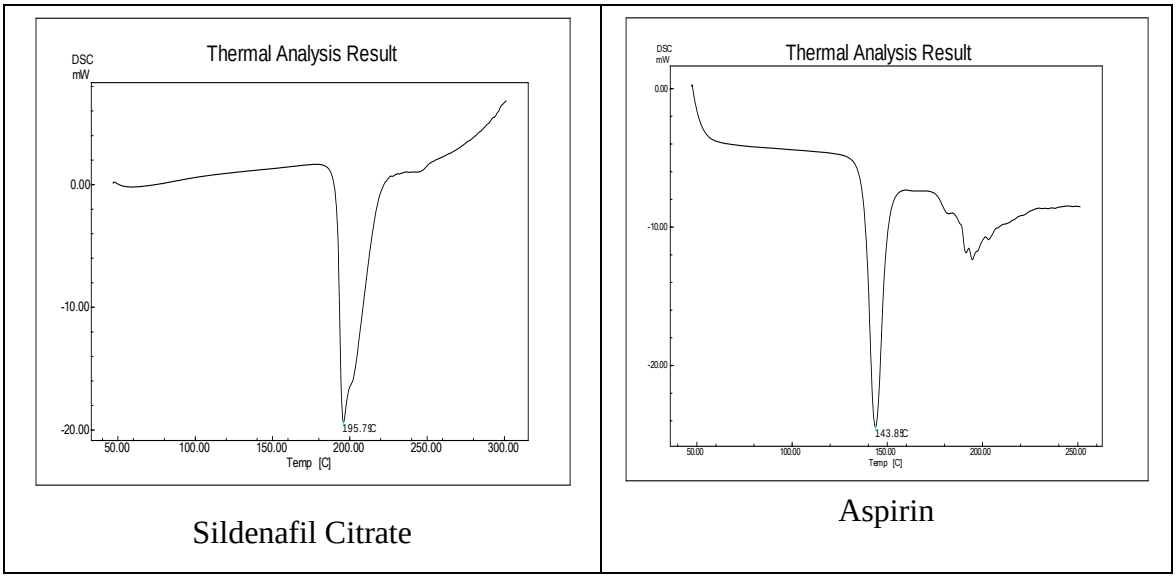


Figure 1: DSC Curve of Sildenafil Citrate and Aspirin

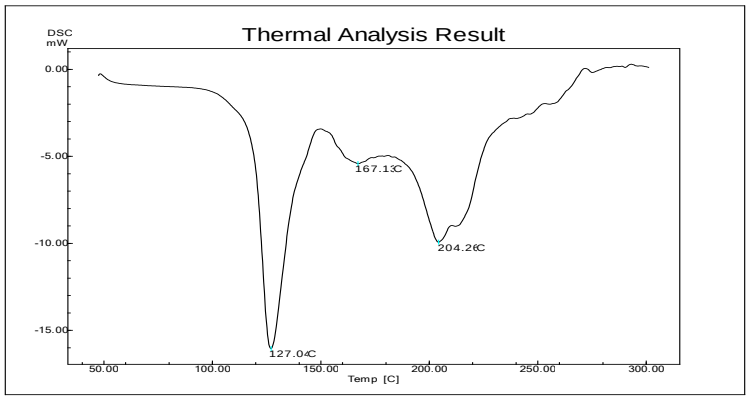
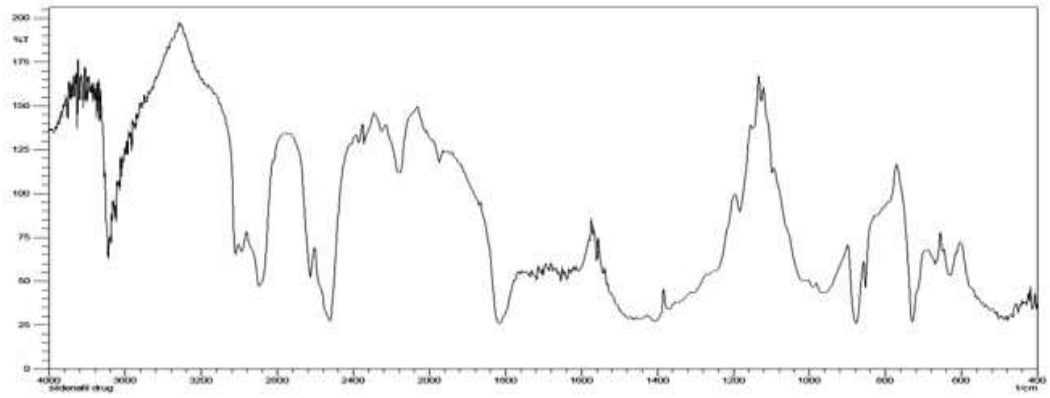


Figure 1.2: DSC Curve of Sildenafil Citrate + Aspirin + Excipients

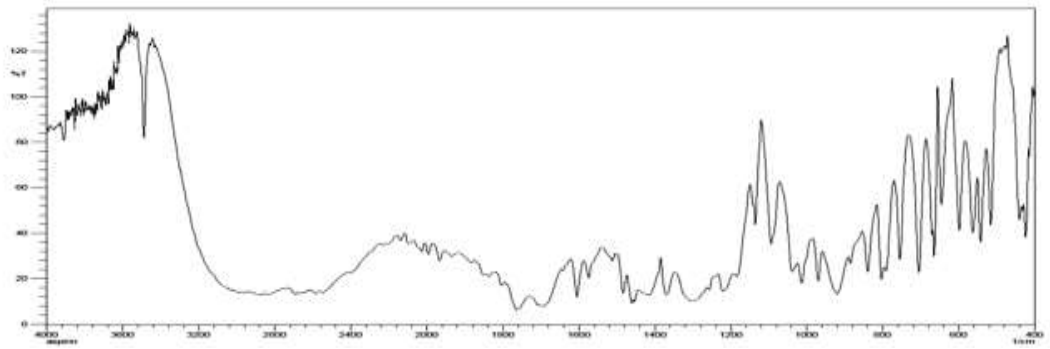
Physical mixture of all above ingredients showed their identical peak at defined temperature range. Presence of all peak indicate that all ingredients are compatible with each other. So we used these ingredients for further project work.

Table 3: Interpretation of IR data for Sildenafil Citrate and Aspirin

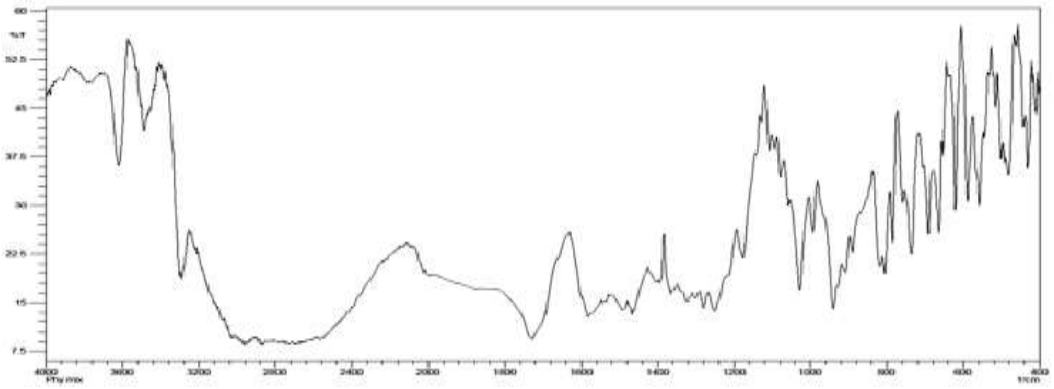
Infrared Absorption Bands of Sildenafil Citrate		**Infrared Absorption Bands of Aspirin**	
Energy (cm^{-1})	**Assignment**	**Energy (cm^{-1})**	**Assignment**
3617	O-H Stretching	2300-2500	Carboxyl O-H
3300	N-H Stretching	1760	Vinyl Ester C=O
3025	C-H Stretching Aromatic	1690	Aromatic Acid C=O
300-2270	C-H Stretching Aliphatic	1610	Aromatic C=C Stretch
1700	C=O Stretching	1580	Aromatic C=C Stretch
1600-1500	C=C Aromatic	1490	Aromatic C=C Stretch
1358, 1173	SO_2 Stretching	1220	=C-O (Acid and Ester)
1252	C-N Stretching	1190	=C-O (Acid and Ester)
		760	O-Subst. Phenyl C-H Bending



Sildenafil Citrate



Aspirin



Sildenafil Citrate + Aspirin + Excipients

Figure 2: FTIR Spectra of Sildenafil Citrate, Aspirin and Sildenafil Citrate + Aspirin + Excipients

The FTIR spectra of drug and excipients shows the characteristic peak of sildenafil citrate and aspirin in figure which is same to that of characteristics peak of sildenafil citrate and aspirin alone. Hence it proves that the excipients used in the formulation are not interacting with the drug and so the formulation is chemically stable.

Calibration Curve of Sildenafil Citrate and Aspirin

Sildenafil Citrate and Aspirin solutions were prepared in distilled water and diluted suitably. The UV spectrums of the solutions were taken on Shimadzu 1700 UV/Vis double beam Spectrophotometer (Japan) and standard curves were prepared as follows. We do not require

the simultaneous equation for the estimation of the Sildenafil Citrate and Aspirin because both the spectra at its wavelength maxima does not cross each other.

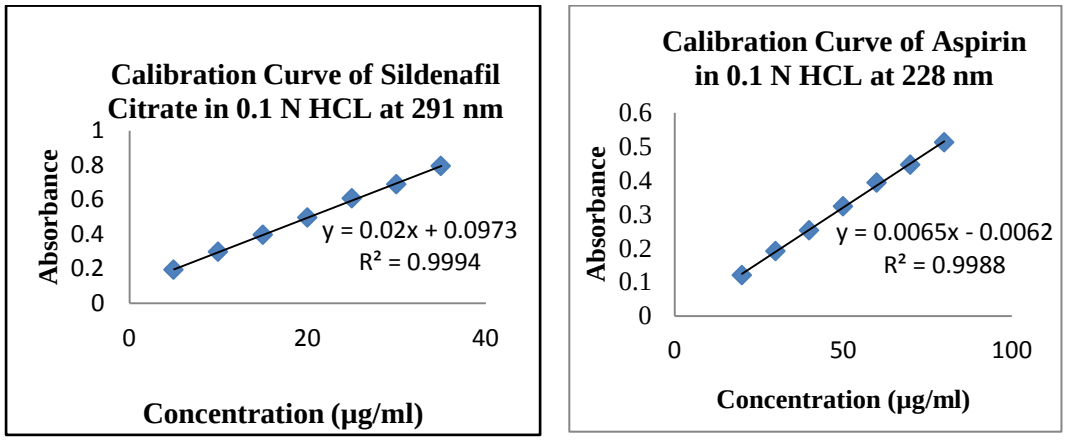


Figure 3: Calibration Curve of Sildenafil Citrate and aspirin respectively.

Evaluation of Granules of 3^2 Full Factorial Design

The granules of all the 9 batches were evaluated for pre-compression parameters. The results for which have been shown in below table no. 6

Table 6: Evaluation of Granules of 3^2 Full Factorial Design

Batch No.	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of Repose (degree)	Carr's Index (%)	Hausner's Ratio
D_1	0.36±0.1	0.39±0.2	24.19±0.2	15.38±0.2	1.15±0.1
D_2	0.38±0.2	0.42±0.15	23.30±0.3	14.44±0.1	1.15±0.1
D_3	0.39±0.4	0.44±0.13	24.23±0.2	13.64±0.3	1.14±0.2
D_4	0.35±0.2	0.38±0.14	25.19±0.5	13.63±0.1	1.15±0.1
D_5	0.38±0.3	0.41±0.13	24.30±0.3	13.43±0.2	1.15±0.1
D_6	0.40±0.4	0.43±0.15	23.22±0.5	13.63±0.3	1.15±0.2
D_7	0.36±0.5	0.38±0.18	25.15±0.6	15.38±0.1	1.18±0.1
D_8	0.39±0.3	0.43±0.13	24.36±0.3	14.06±0.2	1.16±0.3
D_9	0.41±0.2	0.44±0.12	24.27±0.5	14.63±0.1	1.17±0.2

Results presented as mean ± SD

The evaluation results of powder blends were found to be within range for each parameter. The results of angle of repose showed that the good flowability. All the results within range confirmed the suitability of the blend for compression.

Evaluation of Prepared Effervescent Tablet of 3^2 Full Factorial Design

Table 7: Evaluation of Effervescent Tablet of 3^2 Full Factorial Design

Batch No.	Diameter (mm)	Thickness (mm)	Friability Test (%)	Wt. Variation 2853-3487(mg)	Effer. Time (sec)	Hardness (kg/cm^2)	% Drug Content
D_1	25	4.9±0.1	0.72±0.13	3190±158	69±0.2	3.2±1	96±2
D_2	25	4.9±0.1	0.83±0.25	3178±156	68±0.5	3.1±0.9	97±1
D_3	25	4.9±0.2	0.85±0.17	3184±159	66±0.3	3.1±0.7	99±1.7
D_4	25	4.9±0.4	0.77±0.21	3188±157	77±0.6	3.3±0.6	96±3

D_5	25	4.9±0.6	0.82±0.24	3191±155	73±0.8	3.4±0.5	96±2
D_6	25	4.9±0.5	0.86±0.13	3169±154	70±0.4	3.5±0.6	98±2
D_7	25	4.9±0.1	0.85±0.13	3185±159	97±0.5	3.2±0.3	97±4
D_8	25	4.9±0.2	0.76±0.11	3188±157	93±0.2	3.5±0.5	98±5
D_9	25	4.9±0.4	0.81±0.14	3193±155	89±0.9	3.2±0.7	99±2

Results presented as mean ± SD

Effervescence time profile of all batches of effervescent tablet show in table. From these data that prepared tablets gave a better effervescence time. Quantities of acidifying and alkalizing agent are different in all batches so the effervescence time of all batches is different.

Statistical analysis and application of ANOVA

Concerning Y_1 (effervescence time), the results of multiple linear regression analysis showed that the coefficients b_1 bear negative sign and b_2 bear positive sign. The fitted equation relating the response Y_1 to the transformed factor is shown in following equation: $\mathbf{Y_1 = 74.15 - 3.03 (X_1) + 12.67 (X_2) - 0.16 (X_{11}) + 6.18 (X_{22}) – 1.23 (X_1 X_2)}$

The Y_1 for all 9 batches D_1 to D_9 shows good correlation co-efficient of 0.998. Variable X_1 & X_2 has P value < 0.05. So, here both X_1 & X_2 variable significantly affects the effervescence time.

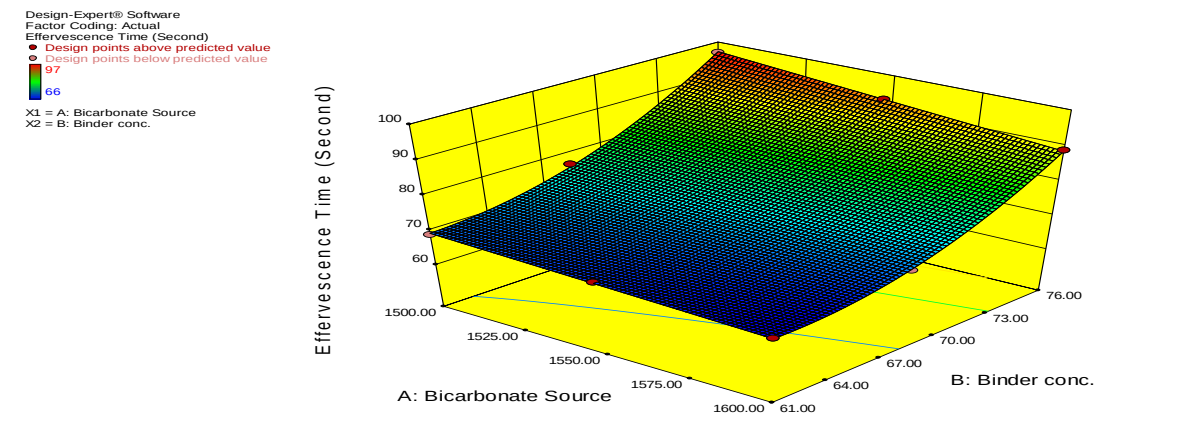


Figure 4: 3-D Surface Plot Show Effect of X_1 and X_2 on Y_1 (Effer. Time)

Figure 4 shows slightly linear, increasing patterns for the values of effervescence time as the concentration of bicarbonate source increase. At high levels of the bicarbonate source, however, the response surface shows a slightly linear shape. Minimum effervescence time is observed at high levels of bicarbonate source.

Concerning Y_2 (binder concentration), the results of multiple linear regression gave the fitted equation relating the response Y1 to the transformed factor is shown in equation, $\mathbf{Y_2 = 3.70 – 0.083 (X_1) + 0.38 (X_2) - 0.017 (X_{11}) – 0.14 (X_{22}) + 0.13 (X_1 X_2)}$ The Y_2 for all 9 batches D_1 to D_9 shows good correlation co - efficient of 0.981. Variables X_1 & X_2 both significantly affects the hardness.

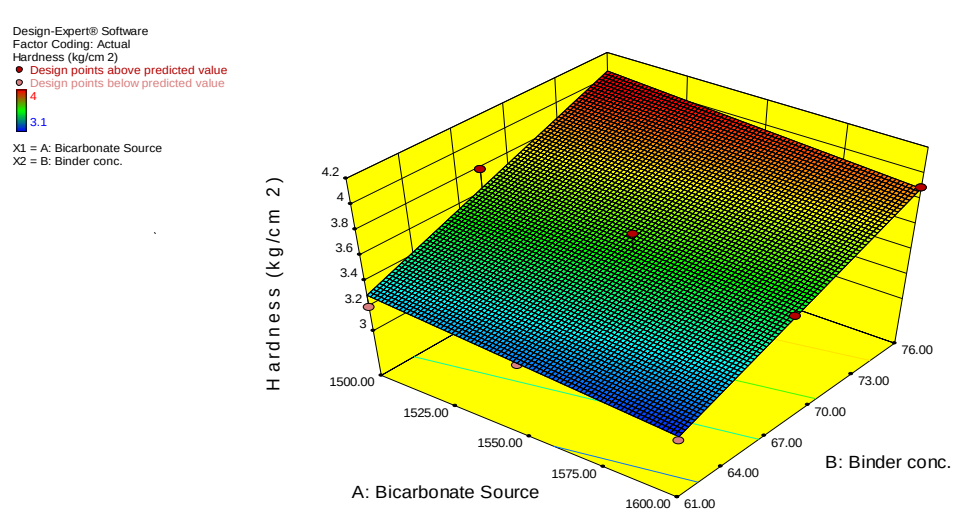


Figure 5: 3-D Surface Plot Show Effect of X_1 and X_2 on Y_2 (Hardness)

Figure 5 shows slightly linear, increasing patterns for the values of hardness as the concentration of binder concentration increase. At high levels of the binder concentration, however, the response surface shows a slightly linear shape. Maximum hardness is observed at high levels of binder concentration.

Optimization of Best Batch from D_1 to D_9 Batches (Effer. Time)

The optimization was based on effervescence time and %cumulative drug release for all the 9 batches.

Comparison of Effervescence time

The results for effervescence time are graphically represented as below figure 6

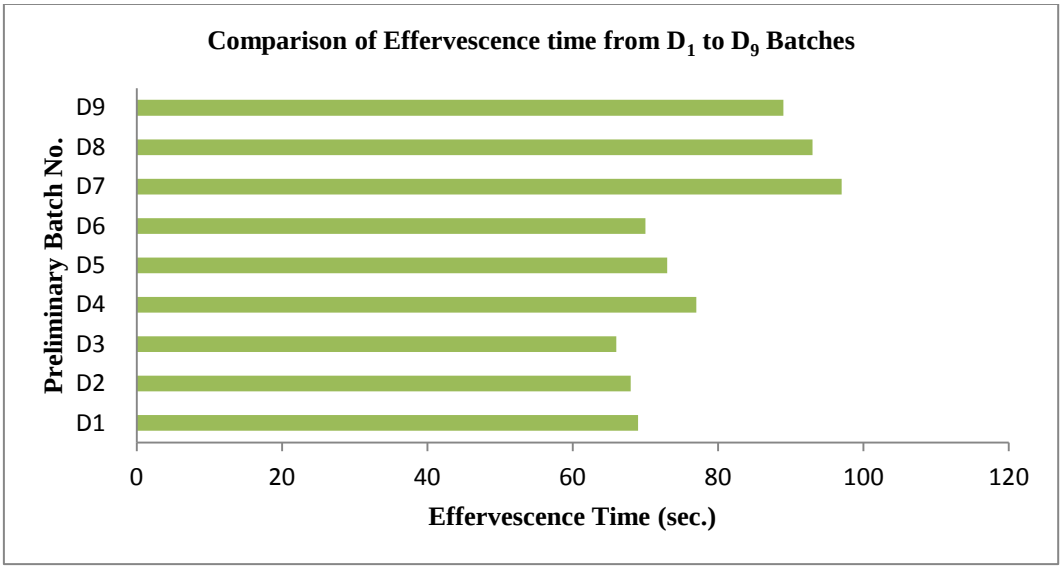


Figure 6: Comparison of Effervescence time from D_1 to D_9 Batches

From the above comparison of effervescence time from D_1 to D_9 batches we can conclude that the D_3 batch is optimized batch because it has less effervescence time amongst the all full factorial design batches.

Dissolution Study of Prepared 3^2 Full Factorial Batches

Dissolution study was performed as per IP in 0.1N Hcl in paddle type dissolution apparatus for 10 hrs. The Dissolution profile of formulations D_1 to D_9 Batches are shown in graph given below.

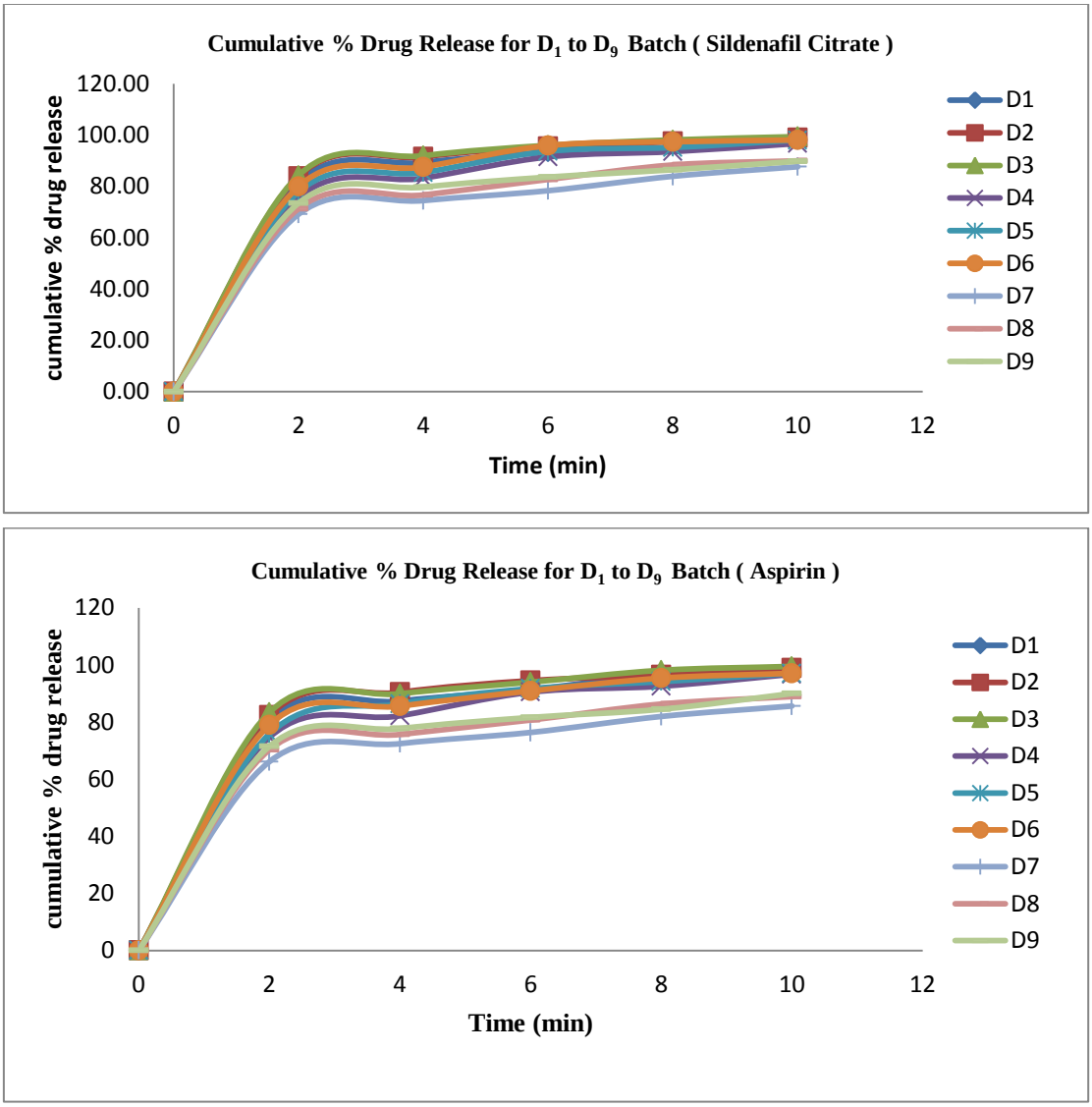


Figure 7: Cumulative % Drug Release for D_1 to D_9 Batch (Sildenafil Citrate and Aspirin)

We can conclude that the D_3 batch having high cumulative % drug release i.e. 99.39% for Sildenafil Citrate and 99.48% for aspirin at the end of 10 min. as compared to other batches. Further we can also conclude that as effervescence time decreases then it will give quick cumulative % drug release. So, from the above result we can conclude that the D_3 batch is our optimized batch because it has good cumulative % drug release.

Stability Study

Accelerated stability study was performed at Temperature 40 ^{O}C and RH 75% for one month and evaluated for cumulative % drug release, % drug content, effervescence time[6, 7.]

Table 8: *In-Vitro* Dissolution of D_3 Batch at Temperature 40 ^{O}C and RH 75%

Parameters	Time	Initial		After 15 Days		After 1 Month	
Cumulative % Drug Release		**Sildenafil Citrate**	**Aspirin**	**Sildenafil Citrate**	**Aspirin**	**Sildenafil Citrate**	**Aspirin**
	0	0.00	0.00	0.00	0.00	0.00	0.00
	2	84.36	83.35	81.74	82.32	83.32	80.76
	4	91.45	89.91	89.35	90.41	91.44	87.35
	6	95.89	93.96	93.32	94.51	95.17	91.35
	8	98.96	98.13	97.61	96.47	96.21	96.63
	10	99.43	99.48	97.67	98.84	97.45	98.11
Drug content(%)	-	99.67	98.31	97.54	97.68	95.12	95.47
Effervescence Time (sec.)	-	**67**		**69**		**70**	

According to table 8 we can conclude that there was no remarkable change in cumulative % drug release, drug content and effervescence time also shown that there was also no remarkable changes in effervescence time.

CONCLUSIONS

In present work an attempt has been made to formulate an effervescent tablet containing immediate release of Sildenafil Citrate and aspirin using various acids-bases and different concentration of binder concentrations with wet granulation using PVP K_{30} in isopropyl alcohol. Based on results of preliminary trials a 3^2 full factorial design was applied and it revealed that the bicarbonate source (X_1) and concentration of binder (X_2) significantly affected the independent variables effervescence time (Y_1) and hardness (Y_2). The D_3 batch was found to be optimum having citric acid 23.65 %, tartric acid 6.30 %, sodium bicarbonate 37.85 %, potassium bicarbonate 12.61 % with binder concentration 2% and hardness adjusted to 3 kg/cm^2. We can conclude that the D_3 batch having high cumulative % drug release i.e. 99.39% for Sildenafil Citrate and 99.48% for aspirin at the end of 10 min. Thus the D_3 batch has desirable property, less effervescence time and enough hardness and immediate release profile.

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