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Original Article

A STATISTICAL APPROACH TO DEVELOPMENT OF TASTE MASKED EFFERVESCENT TABLETS OF SILDENAFIL CITRATE CONTAINING KYRON T134

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ABSTRACT

Objective: The aim of present work was to mask the bitter taste of sildenafil citrate by preparing drug resin complex (DRC) and develop sildenafil citrate 100 mg effervescent tablets.

Methods: Sildenafil citrate and kyron T134 complexes were prepared at different conditions and evaluated for taste and drug loading. Optimized DRC was use to formulate the dispersible tablet by direct compression technique. A 3^2 full factorial design was use to study the effect of effervescent agent (X_1) and croscarmellose sodium (X_2) on dispersion time (Y_1) and wetting time (Y_2). Factorial batches were also evaluated for thickness, hardness, content uniformity, friability, *in vitro* drug release and stability studies. Multiple linear regression analysis, ANOVA and graphical representation of the influence factor by 3D plots were performing by using sigma plot 11.0. A Check point batch was design according to the results of desirability value and evaluated for all the parameter

Results: FT-IR study confirm that sildenafil citrate and kyron T134 were compatible with each other. Among the various DRC batch B29 was found with less bitter and give a more drug loading. Checkpoint batch showed no significance difference between predicted value and actual value for dispersion time and wetting time and it was found stable during stability study.

Conclusion: Sildenafil citrate bitter tast was masked by kyron T134 and full factorial design result was indicate that independent variables have significant effect on dependent variables

Keywords: Taste masking, Ion-exchange resin, Sildenafil citrate, Dispersible tablet, 3^2 full factorial design, kyron T134

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INTRODUCTION

Oral route of drug administration is the most appealing route for the drug delivery but the numbers of orally administered drugs are bitter taste and that creates an unpleasant feeling in the mouth. Therefore, it is necessary to mask the bitterness for enhancing patient acceptability [1, 2]. Ion exchange resins are inexpensive and used to develop a simple, rapid and cost-effective method of taste masking. Ion exchange resins are cross-linked polymers containing salt forming groups in repeating positions on the polymer chain, have an affinity for oppositely charged counter ions, thus adsorbing the ions into the polymer matrix. For immediate release purpose, several ion-exchange resins have been developed for oral administration. Kyron T134 is a derivative of cross-linked polyacrylic polymer used to mask the bitter of medicines. It is also a weak acid derivative of acrylic acid cross-linked polymer having carboxylic acid functional group, which contains K+ionic form [3, 4].

Sildenafil citrate, a selective inhibitor of phosphodiesterase type 5 enzymes (PDE5) and it is use for the treatment of erectile dysfunction. It has extreme bitter taste resulting in poor patient compliance. Conventional sildenafil citrate tablets available in market are not sutable when quick onset of action is required. It needs to be taken before at least 30 min for the desired action due to slow release of the drug. Thus, effervescent tablet can potentially achived rapid onset of desirable action in a convenient manner [5, 6].

The present work was carried out to develop sildenafil citrate 100 mg effervescent tablets, which will mask the bitter test of drug with ion-exchange resin and make the immediate release formulation for quick onset of action.

MATERIAL AND METHODS

Materials

Sildenafil citrate was received as a generous gift from Phanicare chemicals, Hyderabad, India. Kyron T134 was obtaining from Corel pharma chem., Ahmedabad, India. Croscarmellose sodium was purchase from Madhu hydrocolloids Pvt. Ltd., Ahmedabad. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Drug-excipients compatibility study

Drug-excipients interaction plays a vital role in achieving stability of drug in dosage form. Fourier transform infrared spectroscopy (FT-IR) was used to study the physical and chemical interactions between drug and excipients. DSC and FT-IR spectra of sildenafil citrate, kyron T134 and DRC were obtain by using FT-IR instrument. (FT-IR-1700, Shimadzu, Kyoto, Japan). Thermograms of sildenafil citrate and drug-excipients physical mixture were obtain by using an automatic thermal analyzer system (DSC 60, Shimadzu, Japan). The analysis was performed at a rate of 20 °C/min from 50 °C to 300 °C under a nitrogen flow of 25 ml/min [7, 8].

Development and evaluation of drug resin complex (DRC)

In batch process drug resin complex was develop using different process variables. In this process, activated resin was placed in a beaker that containing deionized water. Different ratio of sildenafil citrate and kyron T134 was add and stirred for different periods at various pH as shown in table 3. Batch B1 to B4 was contained sildenafil citrate with different ratio of kyron T134 and stirred for 240 min. Then, the mixture was filter and residue was wash with deionized water. For an optimization DRC was prepared at different pH, temperature, soaking time of resin and stirring time. Batch B5 to B12 was developed at various pH. Batch B13 to B17 was prepared at 40 °C, 50 °C, 60 °C, 70 °C and 80 °C. Batch B18 to B25 was prepared to check the effect of soaking time on drug loading. Using previously optimized conditions batch B26 to B32 was prepared to check the effect of stirring time on drug loading [9, 10]. All batches were evaluated for taste and % of drug loading.

Prepared DRC taste evaluation was done by a panel of 6 volunteers in the age group of 20 to 25 y using time intensity method. Each

volunteer held equivalent to 100 mg sildenafil citrate in the mouth and bitterness were record up to 1 min against pure drug. The yield of DRC was calculated using following equation.

$$\%\text{yield} = \frac{\text{Weight of complex obtained}}{\text{Theoritical weight of complex}} \times 100$$

In vitro drug release of optimized batch DRC was determined using a USP XXIV type II dissolution apparatus. Drug equivalent to 100 mg DRC was add in 900 ml 0.01 M HCl and maintained at 37 °C. Sample was withdrawn at definite time interval and the amount of drug was estimated spectrophotometrically at 292.5. Drug release from the DRC was also perform in deionized water by repeating same procedure [11, 12].

Preliminary trail of sildenafil citrate 100 mg effervescent tablets

Direct compression technique was use to develop sildenafil citrate 100 mg effervescent tablets. Preliminary trail of effervescent tablets were prepared as described in table 1. Preliminary trail batch was prepared to check the effect of effervescent agent and croscarmellose sodium on dispersion time and wetting time. As an effervescent agent Citric acid: Tartaric acid: Sodium bicarbonate (1: 2: 3.44) was taken. All the raw materials were passed through sieve no. 40 and it was mixed in a geometrical order for 15 min. Aerosil, Talc and magnesium stearate were add before compression. Compression was Carry out using flat round shape punch. At the time of manufacturing of effervescent tablets, humidity and temperature was maintained at 25 % RH and 25 °C respectively [13, 14].

Table 1: Preliminary trail of sildenafil citrate 100 mg effervescent tablets

Ingredients	Quantity in mg						
	T1	T2	T3	T4	T5	T6	T7
DRC*	426	426	426	426	426	426	426
effervescent agent #	0	483	580.5	675	750	750	750
Croscarmellose sodium	45	45	45	45	45	30	0
Betacyclodextrin	45	45	45	45	45	45	45
Lactose: Mannitol (50: 50)	898.5	384	286.5	192	132	147	177
Sucralose	30	30	30	30	30	30	30
Dry orange flavor	30	30	30	30	30	30	30
Sunset yellow Color	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil	7.5	15	15	15	15	15	15
Talc	7.5	22.5	22.5	22.5	22.5	22.5	22.5
Magnesium stearate	7.5	18	18	18	18	18	18
Total	1500	1500	1500	1500	1500	1500	1500

*Drug resin complex (DRC) contain Sildenafil citrate 100 mg and kyron T134, #effervescent agent = Citric acid: Tartaric acid: Sodium bicarbonate (1: 2: 3.44)

Evaluation of sildenafil citrate 100 mg effervescent tablets

Bulk density, Tapped density, Carr's index, Angle of repose, Average weight, Thickness, Hardness, Weight variation and % Friability of the effervescent tablets were measured as described by Yadav K *et al.*, Khar RK *et al*, Madgulkar AR *et al.*, and Lakade SH *et al.*, respectively [15-18].

Dispersion time: Dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of deionized water. The time for the tablet to completely disintegrate into fine particles was noted. Six tablets from each batch were randomly selected and dispersion time was recorded.

Wetting time: It was measure by using five circular tissue papers of 10 cm in diameter, which was place in a petridish of 10 cm diameter. 10 ml of eosin solution was adding to the petridish. A tablet was carefully place on the surface of the tissue paper. The time for complete wetting was noted and recorded as the wetting time.

In vitro drug release of effervescent tablets was determined using by USP XXIV type II dissolution apparatus at 100 rpm. A tablet was add to 900 ml 0.01 M HCl for 30 min at 37±0.5 °C. At predetermined time intervals, 10 ml of the sample was collect and replaced with the same volume of fresh medium. Solution was dilute and assay at 292.5 nm using a UV-Vis double beam spectrophotometer.

Taste analysis: All the batches of tablets were subject to gustatory sensory evaluation test performed by a panel of ten volunteers. The volunteers selected randomly and instructed to rate the samples as per the taste evaluation scale [19-20].

Optimization of excipients amount by using 3^2full factorial design

A 3^2full factorial design was use in the present study. Formulation of factorial batches was show in table 2. On the basis of preliminary results, the amount of effervescent agent (X_1) and amount of croscarmellose sodium (X_2) were chosen as independent variables in 3^2 full factorial design, while dispersion time (DT) and wetting time (WT) were taken as dependent variables. Multiple linear regression analysis, ANOVA and graphical representation of the influence of factor by contour plots were perform using sigmaplot 11.0. The experimental runs and measured responses of 3^2 full factorial design batches of sildenafil citrate 100 mg dispersible tablets were deplete in table 7 [21-23].

Table 2: Factorial batches of sildenafil citrate 100 mg effervescent tablets

Ingredients	Quantity in mg								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
DRC*	426	426	426	426	426	426	426	426	426
Effervescent agent	450	450	450	600	600	600	750	750	750
Croscarmellose sodium	30	45	60	30	45	60	30	45	60
Lactose: Mannitol (50: 50)	477	462	447	327	312	297	177	162	147
Sucralose	30	30	30	30	30	30	30	30	30
Dry orange flavor	30	30	30	30	30	30	30	30	30
Sunset yellow Color	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil	15	15	15	15	15	15	15	15	15
Talc	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
Magnesium stearate	18	18	18	18	18	18	18	18	18
Total	1500	1500	1500	1500	1500	1500	1500	1500	1500

*Drug resin complex (DRC) contain Sildenafil citrate 100 mg and kyron T134, #effervescent agent = Citric acid: Tartaric acid: Sodium bicarbonate

(1: 2: 3.44)

Stability study of sildenafil citrate effervescent tablets

Optimized batch was packed in aluminum foil and was placed for stability study at 40˚C/75% RH for 3 mo. Sample was evaluated after 3 mo for physical parameters and *In vitro* dissolution. The dissolution profile of product was compare using similarity factor, f_2, which was calculate by following formula.

$$f_2 = 50 \log [\{1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\}^{-0.5} x100]$$

where log is logarithm to the base 10, n is the number of time points, ∑ is summation over all time points, R_t is the mean dissolution value of the reference profile at time t and T_t is the mean dissolution value of the test profile at the same time point. The USFDA draft guidance document contains more information on similarity factor (f_2). The value of similarity factor (f_2) between 50 and 100 suggests that the two dissolution profiles are similar [24-26].

RESULTS AND DISCUSSION

The powder characteristics of sildenafil citrate like angle of repose, Hausner's ratio and Carr's index showed that drug is poorly compressible and have poor flow properties. So in present study, directly compressible excipient were selected which improved flow property, compressibility and also gives desired drug release.

Drug excipients compatibility study

IR spectra of sildenafil citrate, kyron T134 and DRC are show in fig, 1. The IR spectrum of DRC was found to exhibit some significant difference in the characteristic peaks of sildenafil citrate, revealing modification of the drug environment. As shown in the fig. 1 (A), a peak was observed at 3299 cm^{-1}. IR spectra of DRC showed in fig. 1 (C) shifting of peak this peak from 3299 to 3309 cm^{-1}. Shifting of this peak suggests the formation of new N-H stretching which was previously absent in pure drug. This shows the formation of complex of drug with resin. Thermogram of DSC of sildenafil citrate, kyron T134 and DRC are show in fig. 2. Thermogram of sildenafil citrate showed endothermic peak at 188.64 whereas DRC showed endothermic peak at 188.20 Therefore, there was negligible change in the melting peak of sildenafil citrate. Therefore, it was confirm that sildenafil citrate and kyron T134 were compatible with each other [27, 28].

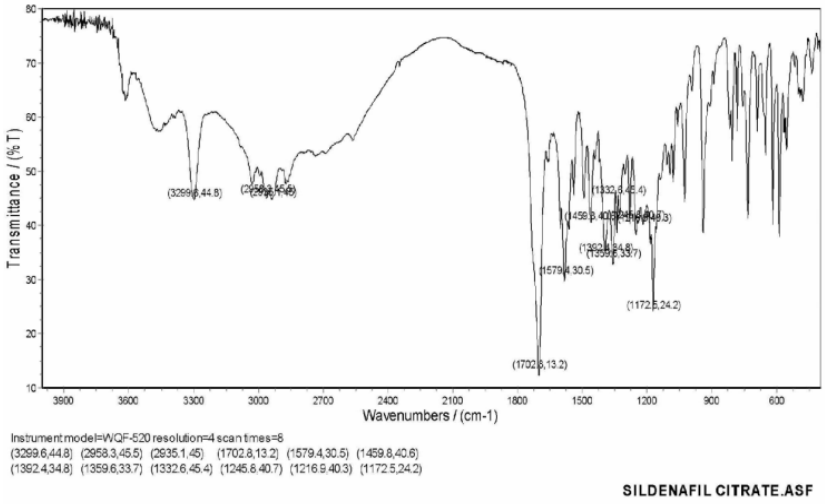

Fig. 1(A): Infrared spectra of sildenafil citrate

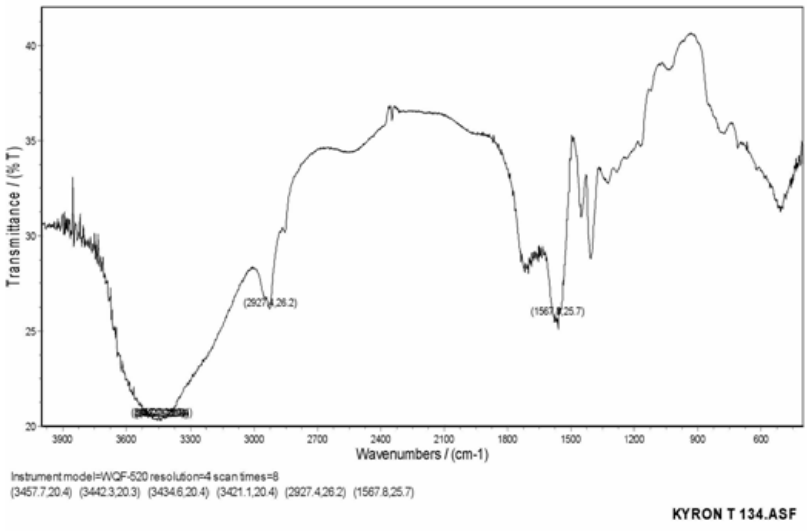

Fig. 1(B): Infrared spectra of kyron T134

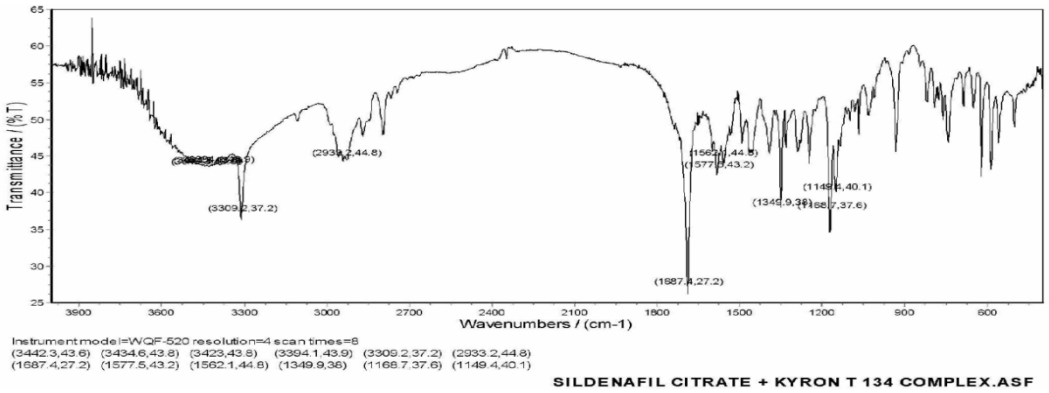

Fig. 1(C): Infrared spectra of DRC

Optimization of drug resin complex (DRC) using different process variables

Drug resin complex was developed by using different process variables. Batch B1 to Batch B4 was prepare by varying the ratio of sildenafil citrate to kyron T134 and drug loading efficiency and bitterness level was observe. From the results, it was clearly reveal that drug loading increases with increase in drug resin ratio. There was no significant difference in drug loading as well as taste, when drug: resin ratio was change from 1:2 to 1:3 and 1:4. Therefore, the drug-resin ratio of 1:2 was use to check the effect of pH on drug loading. pH was shown significant change on drug loading efficiency. There was no change in drug loading when pH was changed from 7 to 9. So, the deionized water used as a medium for further optimization. Here, the effect of temperature on drug loading was measured using drug: resin ratio 1:2 and pH 7. Results showed that there was no significant change in drug loading efficiency on change in temperature. So 30 °C was select for futher study. Batch B19 to B25 was show drug loading was increases with soaking time up to 30 min. There was no significant difference was observe, when soaking time was change from 30 min to 120 min. Thus, the 30 min soaking time was used as optimized time for obtain maximum drug loading. Batch B26 to B32 was prepared to check the effect of stirring time. The result was show that above 240 min drug loading was not increase. Therefore, batch B29 was use for the further studies to prepare sildenafil citrate dispersible tablet.

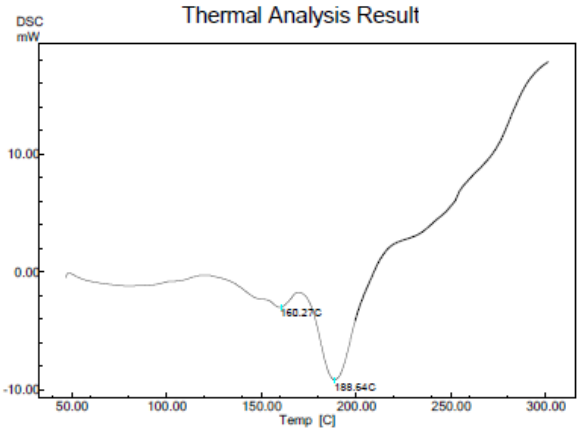

Fig. 2(A): DSC spectrum of sildenafil citrate

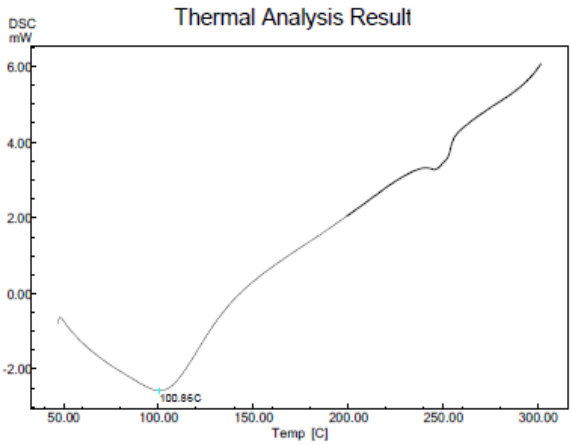

Fig. 2(B): DSC spectrum of kyron T134

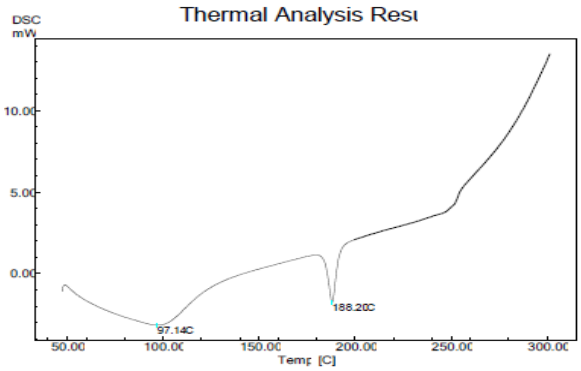

Fig. 2C: DSC spectrum of of DRC

Table 3: Development and evaluation of drug resin complex (DRC)

Batch	Drug: resin ratio	Soaking time (min)	pH	Stirring time (min)	Temp	Taste	% Drug loading
B1	1:1	30	7	240	30 °C	+	74.40±1.09
B2	1:2	30	7	240	30 °C	0	95.59±0.54
B3	1:3	30	7	240	30 °C	0	96.07±0.54
B4	1:4	30	7	240	30 °C	0	97.85±0.54
B5	1:2	30	2	240	30 °C	+	71.14±0.74
B6	1:2	30	3	240	30 °C	+	75.23±0.54
B7	1:2	30	4	240	30 °C	+	84.99±0.94
B8	1:2	30	5	240	30 °C	+	90.23±0.54
B9	1:2	30	6	240	30 °C	+	93.92±0.71
B10	1:2	30	7	240	30 °C	+	95.59±0.54
B11	1:2	30	8	240	30 °C	+	96.06±0.71
B12	1:2	30	9	240	30 °C	+	96.30±0.90
B13	1:2	30	7	240	40 °C	+	95.59±0.54
B14	1:2	30	7	240	50 °C	+	94.75±0.54
B15	1:2	30	7	240	60 °C	+	94.52±0.54
B16	1:2	30	7	240	70 °C	+	93.92±0.71
B17	1:2	30	7	240	80 °C	+	94.16±0.54
B18	1:2	00	7	240	30 °C	+	94.63±0.61
B19	1:2	10	7	240	30 °C	+	78.63±0.69
B20	1:2	20	7	240	30 °C	+	88.80±0.90
B21	1:2	30	7	240	30 °C	+	95.59±0.54
B22	1:2	45	7	240	30 °C	+	95.71±1.07
B23	1:2	60	7	240	30 °C	+	95.94±0.54
B24	1:2	90	7	240	30 °C	+	96.18±0.54
B25	1:2	120	7	240	30 °C	+	95.95±1.09
B26	1:2	30	7	060	30 °C	+	58.56±0.71
B27	1:2	30	7	120	30 °C	+	69.52±0.54
B28	1:2	30	7	180	30 °C	+	85.47±0.74
B29	1:2	30	7	240	30 °C	+	95.59±0.54
B30	1:2	30	7	300	30 °C	+	96.06±0.94
B31	1:2	30	7	360	30 °C	+	96.18±0.54
B32	1:2	30	7	420	30 °C	+	96.30±1.450

++++= Very bitter,+++= Bitter,++= Less bitter,+= Very less bitter

(n=6)

***In vitro* drug release from DRC**

In this study, sildenafil citrate release from drug resin complex was observe in 0.01 M HCl and deionized water separately. In 0.01 M HCl, more than 90% of drug was release within 2 min, whereas in deionized water, less than 15% drug was release within 20 min. *In vitro* drug release from DRC in deionized water was negligible indicating potential application in effervescent tablets. In addition, drug release of almost 100% within 4 min in 0.01 M HCl is favorable for effervescent tablets.

Table 4: Preliminary trail batch evaluation of sildenafil citrate 100 mg effervescent tablets

Batch	Dispersion time(s)	Wetting time(s)
T1	160.66±2.51	43.13±1.15
T2	97.33±1.52	28.66±0.57
T3	89.66±2.08	24.33±0.57
T4	85.33±1.52	21.66±1.15
T5	78.33±1.15	18.33±0.57
T6	74.33±0.57	15.33±0.57
T7	113.33±1.52	34.66±0.57

(n=6)

Preliminary trail batch evaluation of sildenafil citrate 100 mg dispersible tablets

In vitro dispersion time and wetting time of preliminary batches were determined to check the effect of effervescence agents and crosscarmellose sodium. From results shown in table 4, it was clear that amount of effervescence agents and croscarmellose sodium showed significant effects on dispersion time and wetting time of the effervescent tablets. An increase in the amount of effervescence agents and croscarmellose sodium showed significant decrease in dispersion time and wetting time of the tablets. Hence, amount of effervescence agents and crosscarmellose sodium were select as optimize factors for sildenafil citrate 100 mg effervescent tablets. In batch T1, only super disintegrant was use to formulate the tablets without using effervescence agents that showed very high dispersion time and wetting time. This clearly indicates that effervescence agents had the significant effects on both dispersion time and wetting time. Therefore, an effervescence agent was taking as one of the factor for the effervescent tablets. Batch T7 was formulated by using only effervescence agents without super-disintegrant. The results showed increased *in vitro* dispersion time and wetting time. This suggests that super-disintegrant significantly affects the *in vitro* dispersion time and wetting time. Therefore, super-disintegrant was select as another factor for the effervescent tablets. In a preliminary trial, batchs β-cyclodextrin was use to improve the solubility of the drug. However, the drugresin complex did not allow the drug to release in deionize water. The sildenafil citrate and kyron T134 complex was already showed significant drug release in gastric pH. Therefore, β-cyclodextrin was not use in the formulation of factorial batches.

3^2 full factorial design model evaluation

A statistical model incorporating interactive and polynomial terms was use to evaluate the responses:

$$Y=b_0+b_1X_1+b_2X_2+b_{11}X_1^2+b_{22}X_2^2+b_{12}X_1X_2$$

where, Y is the dependent variable, bo is the arithmetic mean response of the 9 runs and any bi is the estimated coefficients for the related factor Xi. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The polynomial terms (X_{12} and X_{22}) are included to investigate nonlinearity. The interaction term "X_1X_2" shows how the response changes when the two factors change simultaneously. Evaluation data of pre-compression and post-compression parameters of factorial batches and *in vitro* % drug release were presented in table 5 and table 6. Table 7 describes the effect of independent variables on dependent variables by 3^2 full factorial designs. The fitted equations (full model) relating the responses that are dispersion time and wetting time to the transformed factor were shown in table 8 and table 9. The polynomial equation can used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). The results of ANOVA suggested that calculated F values for dispersion time and wetting time are 31.38 and 101.57, respectively (table 8). Tabulated F value was found to be 9.013 at $\alpha = 0.05$. Calculated F values are greater than tabulated for all dependent variables therefore factors selected have shown significant effects. From the results of multiple regression analysis, it was found that both factors had statistically significant influence on all dependent variables as $p<0.05$ [29, 30].

Table 5: Factorial batch evaluation of sildenafil citrate 100 dispersible tablets

Batch	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Angle of repose (θ)	Average weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Content uniformity (%)
F_1	0.71±0.02	0.83±0.01	14.25±1.18	28.61°±0.23	1504.25±4.66	2.69±0.02	3.32±0.27	0.73±0.04	101.69±0.75
F_2	0.68±0.05	0.80±0.02	11.04±1.18	29.05°±0.75	1503.25±3.72	2.72±0.02	3.44±0.22	0.73±0.02	101.81±1.30
F_3	0.74±0.07	0.86±0.03	14.81±1.18	28.17°±0.57	1504.0±4.75	2.70±0.01	3.51±0.35	0.76±0.05	103.39±1.10
F_4	0.76±0.06	0.86±0.01	11.53±1.18	29.51° 0.46	1504.0±4.72	2.71±0.01	3.41±0.41	0.85±0.07	101.81±0.72
F_5	0.66±0.02	0.76±0.05	13.33±1.18	27.34°±0.54	1505.0±4.58	2.73±0.02	3.45±0.22	0.72±0.09	101.93±1.79
F_6	0.76±0.03	0.86±0.06	11.53±1.18	27.75°±0.23	1504.25±4.44	2.70±0.01	3.75±0.44	0.82±0.03	102.90±1.09
F_7	0.66±0.02	0.74±0.02	10.0±1.18	27.34°±0.86	1505.0±4.28	2.71±0.03	3.27±0.2	0.69±0.01	102.78±1.16
F_8	0.71±0.06	0.83±0.01	14.25±1.18	26.95°±0.67	1503.75±3.59	2.73±0.03	3.35±0.44	0.66±0.04	103.75±0.91
F_9	0.68±0.05	0.76±0.04	10.34±1.18	26.56°±0.45	1503.5±4.61	2.68±0.03	3.47±0.22	0.59±0.05	101.81±0.36

(n=6)

Table 6: *In vitro* dissolution of factorial batches of sildenafil citrate 100 dispersible tablets

Time (min)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
0	0	0	0	0	0	0	0	0	0
2	82.4±0.59	84.1±0.78	86.3±0.98	87.3±0.81	83.8±1.19	88.6±1.25	84.3±0.45	89.3±1.19	90.5±0.98
4	95.2±1.37	95.7±1.19	96.7±0.81	97.5±0.59	97.1±0.59	97.4±0.67	97.8±0.67	97.9±0.45	98.0±0.22
6	97.6±0.81	98.4±0.60	97.8±1.03	97.8±0.39	98.0±0.81	98.7±0.45	98.2±1.03	98.7±0.45	99.1±0.22
8	98.9±0.39	98.6±0.39	98.4±0.90	98.8±0.98	99.1±0.22	99.3±0.39	99.3±0.39	99.1±0.22	99.6±0.19
10	99.2±0.22	98.9±0.39	99.0±0.36	99.2±0.45	99.6±0.22	99.5±0.59	99.6±0.59	99.3±0.32	99.6±0.07
15	99.3±0.39	99.2±0.22	99.6±0.22	100.0±0.22	99.7±0.78	100.1±0.39	100.0±0.90	99.7±0.39	100.1±0.67
20	99.6±0.22	99.7±0.39	99.6±0.59	100.4±0.22	100.1±0.39	100.6±0.81	100.6±0.45	100.2±0.45	100.4±0.59

(n=6)

Full and reduced model for dispersion time

$$DT = 75.910–(4.900\ X_1)–(6.900\ X_2)+(0.033X_1X_2)+(2.833X_1^2)+(0.750X_2^2)$$

When effervescent agent and croscarmellose sodium was increase dispersion time decrease. From the 3D plot (fig. 3A) and the regression coefficient values of factors, it was concluded that croscarmellose sodium give more significant than effervescent agent. Both the effervescent agent and croscarmellose sodium showed significant effect in the model. Interaction and nonlinearity was not observed. For dispersion time, the significance levels of the coefficients b_{11}, b_{22} and b_{12} were found to be 0.979, 0.098 and 0.440 respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_0, b_1 and b_2 significant at $P<0.05$; hence they were retained in the reduced model. The reduced model for drug dispersion time,

$$DT = 75.910–(4.900\ X_1)–(6.900\ X_2)$$

Table 7: Runs and measured responses of 3^2factorial design batches

Batch	Amout effervescent agent (X_1)	Amount of croscarmellose sodium (X_2)	Dispersion time (Sec) (Y_1)	Wetting time (Sec) (Y_2)
F_1	-1	-1	92.6±3.07	23.0±0.45
F_2	0	-1	84.4±1.35	22.33±0.57
F_3	1	-1	80.0±1.41	20.66±0.87
F_4	-1	0	79.2±1.16	16.66±0.87
F_5	0	0	76.6±1.62	15.33±0.59
F_6	1	0	72.0±1.41	14.66±0.32
F_7	-1	1	76.4±2.05	14.33±0.25
F_8	0	1	72.4±1.01	11.66±0.78
F_9	1	1	66.8±1.60	10.66±0.85
Factors and the levels in the design				
Independent variables		Low (-1)	Medium (0)	High (1)
Amount of effervescent agent (X_1)		450	600	750
Amount of Croscarmellose sodium (X_2)		30	45	60

(n=6)

Table 8: Results of the ANOVA for dependent variables

Source of variation	DF	SS	MS	F value	P value
Dispersion time					
Regression	5	448.030	089.610	31.380	0.009
Residual	3	008.570	002.860		
Total	8	456.600	057.074		
wetting time					
Regression	5	159.550	031.910	101.570	0.002
Residual	3	000.940	000.310		
Total	8	160.500	031.910		

Table 9: Summary of regression output of factors for measured responses

Responses	Model	Coefficient of regression parameters						
		b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
Dispersion time	Full	75.910	–4.900	-6.900	+0.033	2.833	0.750	0.981
	Reduced	75.910	–4.900	-6.900	-	-	-	
wetting time	Full	15.402	-1.335	-4.890	0.222	1.557	0.333	0.994
	Reduced	15.402	-1.335	-4.890	-	1.557	-	

Full and reduced model for wetting time

$$WT = 15.402-(1.335X_1)-(4.890\ X_2)+(0.222\ X_1\ X_2)+(1.557\ X_1^2)-(0.333\ X_2^2)$$

From the 3D plot (fig. 3B) and the regression coefficient values of factors, it was concluded that when effervescent agent and croscarmellose sodium was increase that time wetting time decrease. The results also indicated that the croscarmellose sodium was given a more significant on wetting time. Both the effervescent agent and croscarmellose sodium showed significant effect in the model. Interaction and nonlinearity was not observed. For wetting time the significance levels of the coefficients b_{11} and b_{12} were found to be P= 0.615 and 0.321 respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_1, b_2 and b_{12} was found to be significant at P<0.05; hence, it was retained in the reduced model [31]. The reduced model for wetting time,

$$WT = 15.402-(1.335X_1)-(4.890\ X_2)+(1.557\ X_1^2)$$

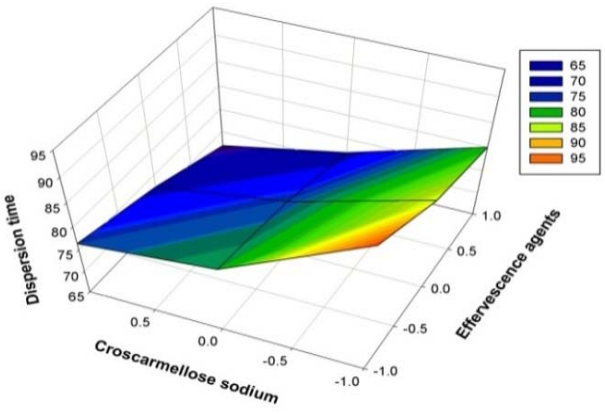

Fig. 3A: 3D plot showing the effect of effervescent agent and Croscarmellose sodium on dispersion time

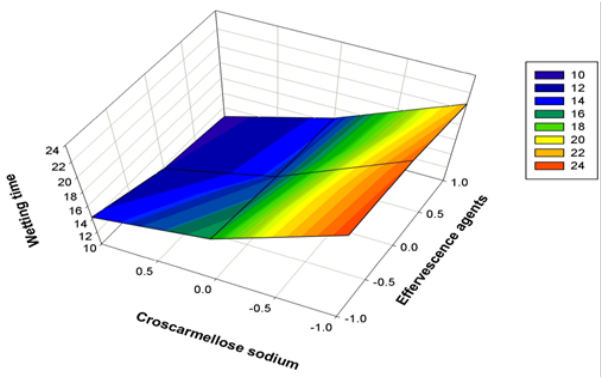

Fig. 3B: 3D plot showing the effect of effervescent agent and Croscarmellose sodium on wetting time

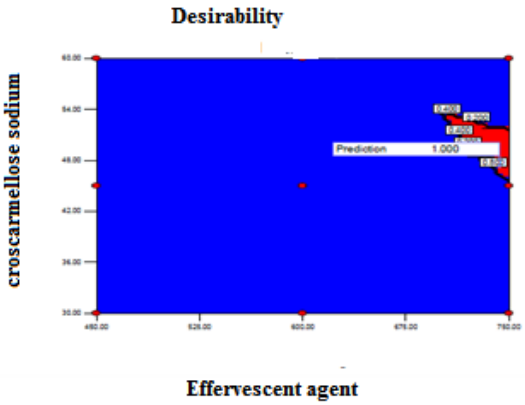

Fig. 3C: Desirability plot

Formulation and evaluation of check point batch

A checkpoint batch was designed accordance to the desirability function as shown in fig. 3C. To validate the evolved mathematical, a checkpoint batch was prepared and evaluated under the same conditions as outlined for the other batches. The response data was compared with predicted data. The application of desirability function gives possibility to predict the optimum levels for the independent variables. In this study, the following constraints were used for the selection of an optimized batch: Dispersion time was 70 to 72 s and wetting time was 10 to 12 s. Desirability plot showed that prediction is 1 when 743.44 mg of effervescence agents and 47.25 mg of Croscarmellose sodium are used. So, checkpoint batch was formulated and validated by using same amount of effervescent agents and Croscarmellose sodium. Results of validation of check point batch are shown in table 10. Results of *in vitro* dispersion time and wetting time showed no significance difference between predicted value and actual value, which suggests that the evolved models may be used for theoretical prediction of responses within the factor space. After short-term stress stability studies check point batch initial *in vitro* release profile was compared using similarity factor, (f_2) value which was found to be 89.50±1.52%. There is no significant difference in similarity factor. Other stability evaluation parameter after 3 mo was shown in table 11. No significant changes were observed in any parameters during the study period, thus it could be concluded that formulation was stable.

Table 10: Formulation of checkpoint batch and comparison with predicted value

Independent variable	Dispersion time (sec)		Wetting time (sec)	
	Predicted value	Actual value	Predicted value	Actual value
X1 (Effervescence agents) =743.44 mg X2 (Croscarmellose sodium)= 47.25 mg	71.27	73±0.45	11.90	12±46

(n=6)

Table 11: Evaluation of checkpoint batch after stability study

S. No.	Parameters	Initial	After 3 mo
1	Appearance	Light orange colour,	No change
2	Hardness (Kg/cm^2)	3.3±0.44	3.4±0.22
3	Friability	0.666 %	0.676 %
4	Dispersion time (Sec)	72.4±1.01	72.8±1.30
5	Wetting time (Sec)	11.66±0.57	12.0±1.0

(n=6)

CONCLUSION

The objective of the present investigation was to formulate, evaluate and optimize the of sildenafil citrate 100 mg dispersible tablets to achieve quick disintegration and fast release of the drug. Kyron T134 was used as taste masking agent that showed highest % of drug loading and test masking. These formulations were evaluated for the parameters like drug excipient compatibility study, thickness, hardness, weight variation, % friability, disintegration test, *in vitro* drug release and accelerated stability studies. Based on preliminary results, the amount of effervescence agents (X_1) and the amount of Crosscarmellose sodium (X_2) were chosen as independent variables in 3^2 full factorial design, while dispersion time and wetting time of the tablets were taken as dependent variables. Multiple linear regression analysis, ANOVA and graphical representation of the influence of factor by 3D plots were performed using Sigma plot 11.0. From the results of multiple regression analysis, it was found that both factors had significant influence on all dependent variables. A Check point batch was design according to the results of desirability value and evaluated for all the parameter. The results of comparison of predicted response and obtained response were found in good agreement. The formulation was found to be stable during accelerated stability study.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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