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Performance Evaluation of Direct Compressible Excipient-Problend (Silicified Microcrystalline Cellulose USP-NF)

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Research Article

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Keywords: Silicified microcrystalline cellulose; Quality by design; Atenolol; Problend; Direct compression; Co-processed excipient

ABSTRACT

The present study carried out to performance evaluation of problend (Silicified Microcrystalline Cellulose USP-NF) for its functionality as diluent. Immediate release tablets of antihypertensive molecule, Atenolol were formulated and studied. Sodium starch glycolate (SSG) was used as disintegrate, Magnesium stearate and talc used as lubricant and glidant respectively. Silicified microcrystalline cellulose (problend) and sodium starch glycolate (super disintegrating agent) were used in different ratios for 3-level full factorial design by design expert (Ver. 12). Quality by Design (qbd) approach was applied to determine material and critical quality attributes. Effect of quantity of problend and SSG was evaluated on chosen responses. Pre-compression blends and tablets were evaluated for various quality parameters.

INTRODUCTION

Direct compression is the preferred method for the preparation of tablets [1]. It offers several advantages [2-3]. No table among them are (i) It is economical compared to wet granulation since it requires fewer unit operations (ii) More suitable for moisture and heat sensitive APIs since it eliminates wetting and drying steps (iii) Changes in dissolution profile are less likely to occur in tablets made by direct compression method on storage than in those manufactured by conventional wet granulations process [4]. This is extremely important because the official compendium now requires stringent dissolution specifications in most solid dosage forms. Disintegration or dissolution is the rate limiting step in absorption in the case of tablets of poorly soluble API developed by wet granulation. The tablets manufactured by direct compression technique disintegrate into particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution [5].

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Direct compression process is mainly influenced by the properties of the excipients. The physico-mechanical properties of excipients that ensure a robust and successful process have good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machinability even in high-speed tableting machinery with reduced dwell times [6].

The majority of the excipients that are currently available fail to give up to these functionality requirements, thus creating the opportunity for the development of new high-functionality excipients. An efficient platform for the manipulation of excipient functionality is provided by co-processing two or more existing excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients [7].

The availability of a large number of excipients for co-processing ensures numerous possibilities to produce tailor-made "designer excipients" to address specific functionality requirements. Co-processed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-mixing, co-drying etc.

Co-processing of excipients in the pharmaceutical industry can be dated back to the late 1980's with the introduction of co-processed microcrystalline cellulose and calcium carbonate [8], followed by Cellactose (Meggle Corp.,Wasserburg, Germany) in 1990, which is a co-processed combination of cellulose and lactose. A similar principle was applied in developing Problend, silicified microcrystalline cellulose (SMCC), which is the most widely used co-processed excipient [9].

The objective of the present study is to evaluate Problend application as directly compressible vehicle in tablet formulations and effect of ratio of Problend and disintegrant on various quality attributes of tablets by Quality by design approach.

Atenolol (ATL) 2-(4-{2-hydroxy-3-[(propan-2 yl) amino] propoxy} phenyl) acetamide, was selected as model drug for this study. ATL is a white or almost white powder with a molecular weight of 266.3361 gm/mol. ATL is slightly soluble in water and sparingly soluble in ethanol. The biological half-life of drug (6 to 8 h) also favors for the development of immediate release formulations [10]. ATL having β-blocker therapeutic category, is used widely in various cardiovascular diseases, e.g., hypertension, angina pectoris, arrhythmias, myocardial infarction and in prophylactic treatment of migraine [11]. It is one of the most commonly used β-blockers for hypertension and angina pectoris [12].

Silicified microcrystalline cellulose (SMCC) [Co-processed microcrystalline cellulose (98%w/w) and colloidal silicon dioxide (2% w/w)] is used to improve compaction and blending properties both in wet granulation and direct compression [6].

Sodium starch glycolate (2-8%) is used as disintegrant in oral pharmaceuticals prepared by either direct compression or wet-granulation processes. It helps in disintegration by rapid swelling and wicking upon contact with water. Wicking is a "whipping" action where material-water interface replaced the material-air or material-material interface spontaneously and helps in maintaining capillary flow [8].

The application of Design of Experiments (DoE) in the pharmaceutical industry is becoming a mandatory as one of the most important development and optimization tool in recent times. It uses a simple experimental design to screen and optimize a number of experimental parameters in formulation development. DoE provides maximum information about the design with fewer initial experiments or trials.

MATERIALS AND METHODS

Atenolol, Problend were obtained as gift samples from Gangwal Chemicals Private Limited, Mumbai. Sodium starch glycolate and Magnesium stearate were purchased from Loba Chemie Pvt. Ltd., Mumbai. Purified Talc was purchased from Arora Pharmaceuticals Private Limited, Delhi.

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Development of Atenolol immediate release (IR) tablets

Atenolol and Sodium starch glycolate co-sifted through ASTM 60# sieve, thrice. Transfer co-sifted mixture to blender. Transfer Problend and Filler (microcrystalline cellulose) to the blender. Blend for 15 min at speed of 10 rpm. To this blend add lubrication quantities of pre-sifted (through ASTM60# sieve) magnesium stearate and purified talc. Lubricate for 3 min at 10 rpm.

Pre-compression blends were evaluated for flow properties. This uniformly mixed blends were compressed into tablets by using rotary tablet press containing 50 mg ATL using 7 mm round flat bevelled surface punches by direct compression method. Total weight of tablet was kept 200 mg. The composition of various tablet batches and the factorial design batches are as shown in Table 1.

Table 1. Composition of different Atenolol tablet formulations.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Atenolol	50	50	50	50	50	50	50	50	50	50	50	50	50
ProBlend	87.5	100	87.5	100	75	87.5	87.5	75	75	100	87.5	87.5	87.5
Sodium starch glycolate	8	4	8	4	12	8	8	12	12	4	8	8	8
Filler	10.5	2	10.5	2	19	10.5	10.5	19	19	2	10.5	10.5	10.5
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Purified Talc	2	2	2	2	2	2	2	2	2	2	2	2	2
Tablet weight	160	160	160	160	160	160	160	160	160	160	160	160	160

Evaluation of pre-compression blends

Pre-formulation blends were evaluated for physical parameters. The powder properties include bulk density, tapped density, Carr's index, Hausner ratio and angle of repose was determined by procedure reported in United States Pharmacopoeia.

Evaluation of Atenolol tablets

All the batches of tablets were evaluated for various post-compression parameters like weight variation, friability, and hardness, wetting time, drug content, disintegration and dissolution [13-18].

Wetting time

Wetting times were assessed by determining the time required for a tablet to completely take up water and be visually wetted throughout to the surface. Blue 1 dye was dissolved in slightly heated DI water (37 ± 0.5 °C) to create a 0.1% (W/W) dye solution. Using a dye solution instead of plain DI water made visual evaluation of the endpoint much easier. The types of materials with their dimensions and the volumes of dye solution used during the test are shown in Table 2.

Table 2. Details for test parameters of Table.

Type of material	Dimension	Volume of 0.1% blue 1 solution (mL)
Whatman circular filter	2.50 cm diameter (layered 5 times)	2.5

Wetting test was conducted in a 10 cm internal diameter petri dish. Whatman filter paper of 2.50 cm diameter size used for the test. During the test whatman filter paper was placed within the petri dish and the dye solution was added on Whatman filter paper stack using 2.5 ml calibrated pipette. Volumes of 2.5 ml dye solution were used to simulate the oral cavity. A tablet was then placed on the wet filter paper using forceps and the wetting time was recorded using a stopwatch.

Disintegration time

Tablet disintegration time was measured according to United States Pharmacopoeia method with a disintegration tester (Veego India). Disintegration time was determined for each tablet.

In-vitro drug release study

In-vitro drug release of Atenolol tablets was carried out using Electro lab USP II dissolution testing apparatus at 50 rpm. The dissolution test was carried out using 900 ml of 0.1 N Acetate buffer pH 4.6. Aliquots of 5 ml were withdrawn at preselected time intervals (5, 10, 15 and 30 min) and replaced with fresh medium to maintain sink condition. Withdrawn sample were analyzed spectrophotometrically at 276 nm using Shimadzu 1700 double beam UV-Visible Spectrophotometer.

Drug content

Twenty tablets were selected randomly and crushed to powder. A quantity of this powder corresponding to average tablet weight was dissolved in 100 ml of dissolution medium, stirred for 15 min and filtered. 1 ml of filtrate was diluted to 100 ml with dissolution medium. Absorbance of this solution was measured at 276 nm using dissolution medium as blank and drug content in sample estimated.

Full factorial design

A two factor, three-level full factorial design (3^2) was employed for optimization of tablets. The concentration of Problend (a) and SSG (b) were selected as independent variables. Concentration of Problend was evaluated at 75 mg, 87.5 mg, and 100 mg per tablet weight and the concentration of SSG was evaluated at 4 mg, 8 mg and 12 mg per tablet weight. The disintegration time was selected as response (i.e. dependent variables). Design Expert 12.0.8.0 Software (Stat-Ease Inc., USA) was used for the generation and evaluation of statistical experimental design. The Factorial design builds Information as shown in Table 3. The Factors and coded range of factorial design are shown in Table 4. Responses selected for study design shown in Table 5.

Table 3. Factorial design build Information.

Factorial design build Information			
File Version	12.0.8.0		
Study type	Response surface	Subtype	Randomized
Design type	3 Level factorial	Runs	13.00
Design model	Quadratic	Blocks	No blocks
Build time (ms)	199.00		

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Table 4. The Factors and coded range of factorial design.

Factor	Name	Units	Type	Minimum	Maximum	Coded low	Coded high	Mean
A	Problend	mg	Numeric	75.00	100.00	-1 ↔ 75.00	+1 ↔ 100.00	87.50
B	SSG	mg	Numeric	4.00	12.00	-1 ↔ 4.00	+1 ↔ 12.00	8.00

Table 5. Responses for factorial design study.

Response	Name	Units
R1	Disintegration time	Sec

RESULTS AND DISCUSSION

Pre-compression blend evaluation

Preformulation parameters of all formulations F01 to F13 were evaluated i.e. Bulk density, Tapped density, Hausner's ratio, Angle of repose and shown in Table 6. The results confirmed that all batches exhibited good flow properties as well as packing characteristics. From the results it is clear that quantity of Problend as diluent/filler is satisfactory. At all levels studied all physical parameters were found satisfactory.

Table 6. Pre-compression blend evaluation: Bulk density, tapped density, angle of repose and Hausner's ratio of formulations (n=3).

Sr. No.	Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's index	Angle of repose
1	F1	0.54	0.64	1.19	15.97	29.46
2	F2	0.57	0.66	1.15	13.04	29.36
3	F3	0.55	0.66	1.20	16.67	31.98
4	F4	0.58	0.67	1.16	13.79	31.05
5	F5	0.53	0.67	1.26	20.63	32.90
6	F6	0.56	0.66	1.18	15.25	31.96
7	F7	0.55	0.65	1.19	15.97	31.96
8	F8	0.52	0.65	1.25	20.00	30.97
9	F9	0.53	0.66	1.24	19.35	32.4
10	F10	0.58	0.67	1.15	13.04	28.55
11	F11	0.54	0.65	1.20	16.67	31.01
12	F12	0.56	0.67	1.19	15.97	32.09
13	F13	0.55	0.65	1.18	15.25	31.95

For all the formulations bulk densities were observed between 0.52 to 0.58 g/ml. Ideally 0.5 g/mL bulk density is desired for pharmaceutical powders. The investigated model drugs (Atenolol) exhibited poor flow properties in comparison to the examined pre-compression blends prepared using Problend. Hausner ratio>1.4 indicates that Atenolol has very cohesive nature. Powder flow properties of blends F1 to F13 were also found within acceptable limits as Hausners ratio value is ranging from 1.15 to 1.26 suggesting free flowing to fairly flow to pre-compression blends. Similar observation was found for Carr index as well. Carr index values ranging from 13.04 to 20.63. Powder flow is measured in angle of repose value. Values from 25 to 30 shows excellent powder flow and 31 to 35 depict good powder flow property. For the studied blends angle of repose values observed ranging from 28–33 showing excellent to good flow properties. All these above values are extremely desirable for direct compression. Flowability is required in order ensure homogeneous and rapid flow of powder for uniform die filling. During the short dwell-time (milliseconds), the required amount of powder blend should be transferred into die cavities.

Post-compression parameters for Atenolol tablets

The parameters of all formulations F01-F13 were evaluated and found within pharmacopeial limits. The Average weight, thickness, hardness, drug content and friability values of all formulations are shown in Table 7. From the results it is clear that Problend is giving satisfactory tableting properties of blends. Satisfactory direct compression achieved in all studied formulations and at all levels of Problend as well. At all levels studied all physical parameters were found satisfactory.

It was observed that all the tablet formulations passed the test for weight variation, as the percentage of weight variation was within the pharmacopeial limits. The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness in the range of 5.0 to 7.0 kg/cm^2. The tablets mean thickness was almost uniform, between 3.12 and 3.15 mm in all formulations. Friability varied between 0.13% and 0.25%. Friability values less than 1% were an indication of good mechanical resistance of tablets. The drug content in all formulations was highly uniform and in the range of 99.72%-101.31%. The results of the evaluation parameters of the tablets are depicted in Table 7.

Table 7. Average weight, thickness, hardness, drug content and friability of formulated tablets.

Sr. No.	Formulation code	Avg. wt. (mg)	Thickness (mm)	Hardness (kg/cm^2)	Drug content (%)	Friability (%)
1	F1	161	3.12	6.11	99.30	0.18
2	F2	160	3.19	6.60	99.88	0.14
3	F3	160	3.12	6.22	99.78	0.19
4	F4	162	3.18	6.51	98.89	0.15
5	F5	160	3.10	5.46	100.11	0.22
6	F6	161	3.12	5.92	99.11	0.21
7	F7	160	3.13	6.04	99.62	0.18
8	F8	160	3.10	5.62	99.25	0.23
9	F9	160	3.11	5.70	99.10	0.23
10	F10	162	3.18	6.65	98.15	0.15
11	F11	160	3.14	6.11	99.21	0.20
12	F12	161	3.13	6.07	98.44	0.18
13	F13	161	3.12	6.20	99.73	0.19

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Wetting time

It is an important criteria for determining the capacity of disintegrants to show its effect in presence of little water. By using different concentrations of superdisintegrant and Problend, the wetting time in formulations F01 to F13 are found to be in range of 46 sec to 131 sec respectively as shown in Table 8. The results indicate that all the formulation has quick water absorption tendency and hence minimum wetting time which indicates less time for tablet to disintegrate.

In-vitro disintegration time

The disintegration time was used as a response during formulation optimization for evaluation of IR tablets of Atenolol. The USP disintegration method was used to determine the disintegration time for formulation F1 to F13. The disintegration time according to USP method and wetting time were then compared. The results of this test are shown in Table 8. It can be seen that wetting times and disintegration times closely correlated with each other. In the cases where there is significant difference between two values i.e. wetting time and disintegration time, swelling behavior of disintegrant is playing role. In wetting time study only 2.5 ml of dye solution was available which is absorbed in the filter papers in petri dish. This 2.5 ml dye solution is not completely available for tablet. Part of dye solution taking part in swelling process slowing down the surface wetting of tablet. Since the USP disintegration test requires a significantly larger amount of water (900 ml) to be used, swelling had an insignificant retarding effect on disintegration process. The results conclude that with the increase in concentration of superdisintegrant disintegration time has decreased.

Table 8. Wetting time and *in-vitro* disintegration time of Atenolol tabolets.

Formulation code	Wetting time (sec.)	*In-vitro* disintegration time (sec.)
F1	74	78
F2	138	127
F3	78	80
F4	130	118
F5	49	45
F6	80	75
F7	78	81
F8	46	42
F9	51	48
F10	134	130
F11	82	85
F12	76	79
F13	82	86

In-vitro dissolution study

The *in-vitro* dissolution studies of all formulations (F1 to F13) were conducted and the results shown in Table 9. From dissolution study, it was observed that during dissolution, the tablets initially swelled and eroded over period of time. The results conclude that Problend supported swelling and disintegration of tablet during dissolution. In all the formulations tablets prepared gave rapid dissolution of the atenolol i.e.>80% drug release in 30 min.

Table 9. Cumulative% drug release for formulations.

Time (min)	5	10	15	30
F1	79.16	91.16	96.83	97.16
F2	78.66	88.16	98.33	102.66
F3	78.22	90.16	98.15	95.33
F4	76.66	87.69	97.33	102.5
F5	84.21	93.1	98.45	102.26
F6	79.21	92.14	98.39	98.39
F7	79.25	90.35	97.11	99.36
F8	83.81	94.5	98.1	100.2
F9	85.33	94.33	98.16	103.83
F10	75.33	89.66	98.56	100.83
F11	78.22	91.11	98.12	99.25
F12	80.17	92.66	97.83	98.66
F13	79.21	90.12	97.14	99.21

Figure.1 showed the dissolution profile of Atenolol tablets formulations F1 to F13 according to the DoE design. Upon studying the effect of the chosen factors on drug release, it can be concluded that the first factor which is the quantity of Problend in formulations affected the dissolution rate but significant difference is not observed for all the levels studied. All the formulations showed more than 75% drug release observed in initial 5 min and more than 90% drug release within 30Min which is highly desirable for immediate release dosage forms. Very slight difference in drug dissolution in initial 5 min can be attributed to the disintegration time of all formulations and hence the quantity of superdisintegrant added per formulation. It is clearly seen that formulations where 12 mg SSG is present are showing faster dissolution as compared to other formulations. For better understanding dissolution profiles of similar formulations were compared. Also average values form each set (Formulation F5, F8 and F9 having 75 mg Problend and 12 mg of SSG), (formulation F1, F3, F6, F7, F11, F12 and F13 having 87.5mg of Problend and 8 mg of SSG), (formulation F2, F4 and F10 having 100 mg Problend and 4 mg of SSG) of experiment calculated and plotted to see the effect of Problend and SSG on dissolution profile. In each set of experiments overlapping dissolution profiles can be seen depicting formulation robustness. Also dissolution profile of average value of each set compared which clearly indicate the difference in drug release in initial 5 min time point.

The observed value of response (disintegration time) was further analyzed statistically to evaluate the effect of various factors and interaction of factors using Design Expert Software version 12.0 Data shown in Table 10. The analysis was performed using Quadratic model of 3-level full factorial design using Design Expert Software version 12.0.

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Figure 1. Dissolution profile of formulations F1 to F13 as per experiment sets. a) Dissolution profiles of F5, F8 and F9 having 75 mg Problend and 12 mg SSG in formulations. b) Dissolution profiles of F1, F3, F6, F11, F12 and F13 having 87.5 mg Problend and 8 mg SSG in formulations. c) Dissolution profiles of F2, F4 and F10 having 100 mg Problend and 4 mg SSG in formulations. d) average dissolution profiles of three experimental sets.

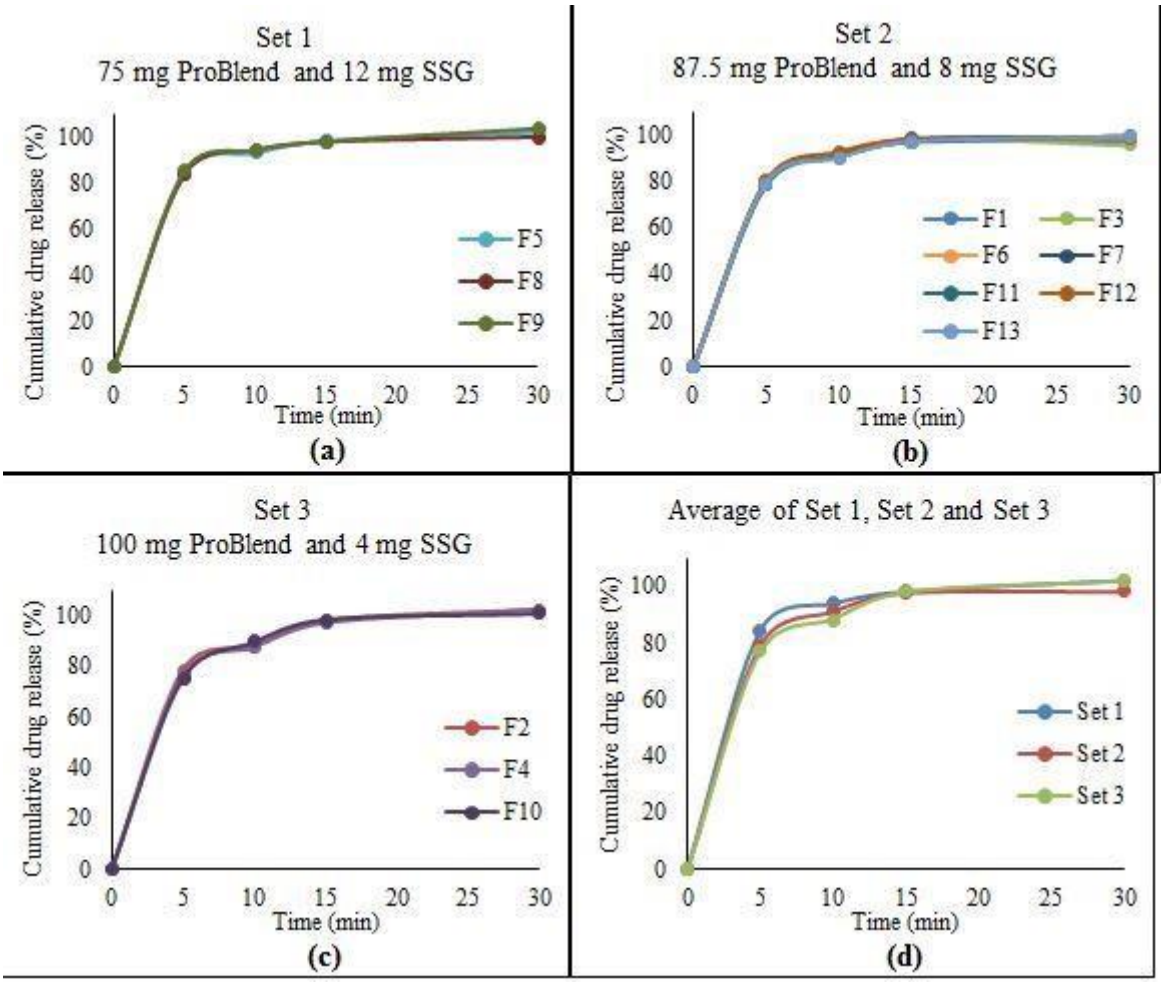

Table 10. Effect of variables on disintegration time using 3-level full factorial design.

		Factor 1	Factor 2	Response 1
Std	Run	A:Problend (Quantity in mg)	B:SSG (Quantity in mg)	Disintegration time (s)
7	1	75	12	40
1	2	75	4	110
4	3	75	8	50
8	4	87.5	12	42
3	5	100	4	115
12	6	87.5	8	55
5	7	87.5	8	57
10	8	87.5	8	59

2	9	87.5	4	113
11	10	87.5	8	56
6	11	100	8	68
13	12	87.5	8	58
9	13	100	12	45

Design Expert 12.0 software was used to apply ANOVA on disintegration time so as to examine the relevance and the implication of model under scanner Table 11. The data from multiple regressions has shown that square terms should be maintained in mathematical model to elucidate the response curvature. The Predicted R^2 of 0.9624 is in reasonable agreement with the Adjusted R^2 of 0.9966; i.e. the difference is less than 0.2. Adeq. Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 59.851 indicates an adequate signal. This model can be used to navigate the design space. The F-value and p-value demonstrate that whether the model is significant or non-significant. The Model F-value of 497.90 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

Table 11. ANOVA for process variables.

Source	Sum of squares	DF	Mean square	F-value	p-value	
Model	8893.55	7	1270.51	497.90	<0.0001	significant
A-Problend	162.00	1	162.00	63.49	0.0005	
B-SSG	2520.50	1	2520.50	987.76	<0.0001	
AB	0.0000	1	0.0000	0.0000	1.0000	
A^2			2.96	1.16	0.3310	
B^2			1053.93	413.03	<0.0001	
A^2B			0.3333	0.1306	0.7325	
AB^2			56.33	22.08	0.0053	
A^3	0.0000	2.96	1			
B^3	0.0000	1053.93	1			
Residual	12.76	0.3333	1			
Lack of fit	2.76	56.33	1	1.10	0.3528	not significant
Pure error	10.00	4	2.50			
Cor total	8906.31	12				

P-values less than 0.0500 indicate model terms are significant. In this case A, B, B^2, AB^2 are significant model terms. Values greater than 0.1000 indicate that the model terms are not significant. The p-value (<0.0001) has revealed that model is significant.

The polynomial equation for disintegration time is shown below:

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Disintegration time=+57.28+9.00A–35.50B+1.03A^2+19.53B^2+0.5000A^2B–6.50 AB^2

Where,

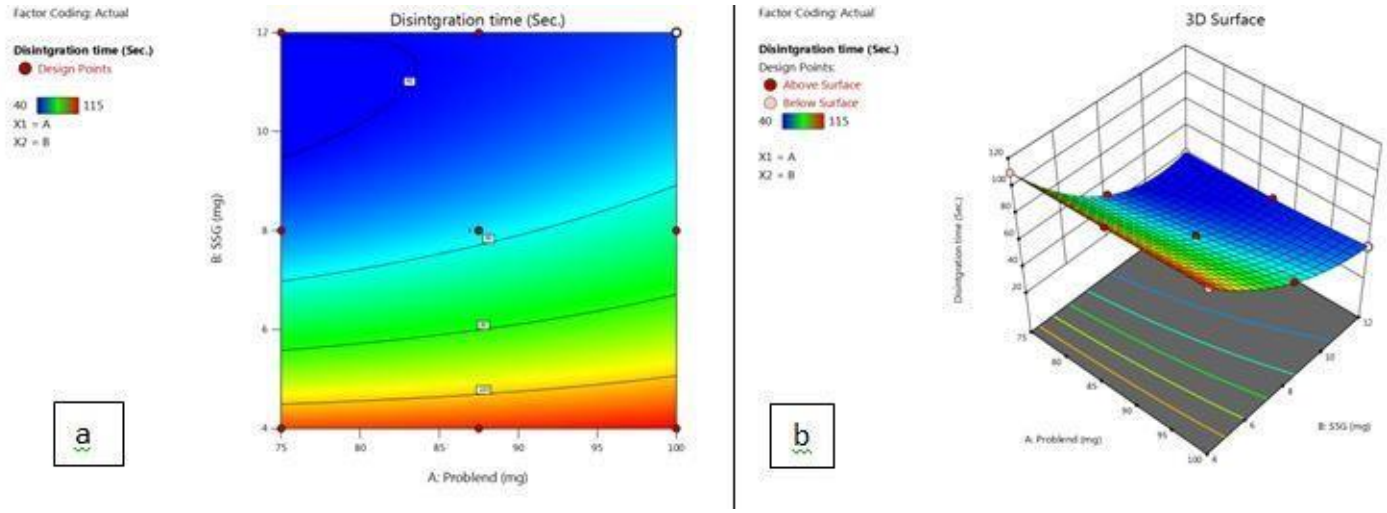
A=Problend, B=Sodium starch glycolate, AB=Show interaction term, A^2 and B^2 are quadratic relationship terms.

The negative values of coefficient estimates B, AB^2 specify that disintegration time of Atenolol tablets increased with respect to decrease in corresponding variable.

The positive values of coefficient estimates A, A^2, B^2, A^2B clearly demonstrate that disintegration time of Atenolol tablets increased with respect to increase in corresponding variable.

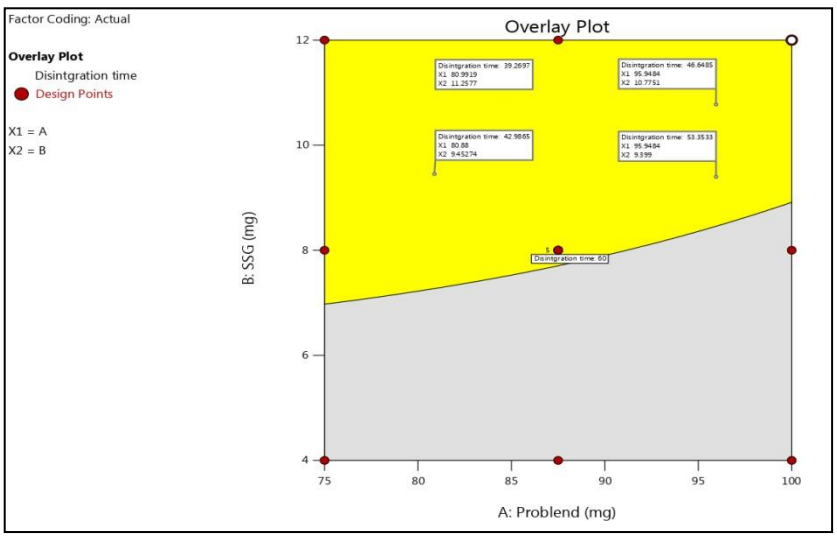
The effect of different factors on disintegration time was determined by polynomial equation, contour plot Figure 2a and 3D response surface plot Figure 2b, constructed using Design Expert software (Version 12.0, Stat-Ease Inc., and Minneapolis, MN).

Figure 2. The Main effect of independent variables on disintegration time (a) contour plot and (b) 3D response surface plot.



The overlay plot demonstrated that the formulation containing Problend 96.026 mg and SSG 9.3 mg would be selected to achieve the targeted disintegration time, taken as dependent variable using Quadratic model of 3-level full factorial design by Design Expert version 12 Figure 3.

Figure 3. The Main effect of independent variables on disintegration time by overlay plot.



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Formulation of optimization using polynomial equation

Formulation using silicified microcrystalline cellulose (SMCC) of different manufacturers: Three formulations A, B and C were manufactured using different samples of SMCC from different manufacturers like Formulation A using Problend form Gangwal chemicals, Formulation B using competitor 1 and Formulation C using competitor 2 respectively.

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Evaluation of optimized formulations

Pre-compression parameters: The determined values of pre-compression parameters are shown in Table 12. Formulation A shows better results than formulation B and C. The results demonstrate that blend prepared with Problend has shown good flow properties than the blends prepared SMCC from competitor 1 and competitor 2.

Table 12. Bulk density, Tapped density, Angle of repose, and Hausner's ratio of formulations A, B and C (n=3) Mean ± S.D.

Sr. No.	Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Angle of repose
1	A	0.58	0.71	1.22	31.54
2	B	0.55	0.71	1.28	32.06
3	C	0.58	0.76	1.31	32.96

Post compression parameters: Various post compression parameters were determined for formulation A, B and C and values shown in Tables 13 and 14. Formulation A shows better results than B and C. The formulation A and C have almost same thickness and formulation B has less thickness but formulation A shows less friability than formulation B and C. The hardness of formulation C is less than A and C.

Table 13. Average weight, thickness, hardness and friability of formulated tablets A, B and C.

Sr. No.	Formulation code	Avg. wt. (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
1	A	200.4	3.12 ± 0.04	2.6 ± 0.21	0.479
2	B	200.2	3.10 ± 0.06	2.8 ± 0.46	0.481
3	C	200.6	3.12 ± 0.06	2.5 ± 0.22	0.485

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Table 14. Wetting time, disintegration time and drug content of formulated tablets A, B and C.

Sr. No.	Formulation code	Wetting time (Sec.)	Disintegration time (Sec.)	Drug content (%)
1	A	38.21	40.58	99.12 ± 0.14
2	B	40.02	43.22	98.89 ± 0.18
3	C	40.44	41.20	98.78 ± 0.16

***In-vitro* drug release:** Values of *in-vitro* drug release study of formulations A, B and C are shown in Table 15 and represented in Figure 4. Although there are little variations in dissolution profiles, results indicate that formulation A (Using Problend) shows maximum cumulative drug release of 86.52%. The results conclude that Problend as filler has shown little effect on mechanical strength of tablets than formulation B and formulation C. The results demonstrate that drug released faster from formulation Problend as compared to formulation using SMCC from competitor 1 and competitor 2.

Figure 4. Graph between% CDR V/S time (min) of formulations A, B and C.

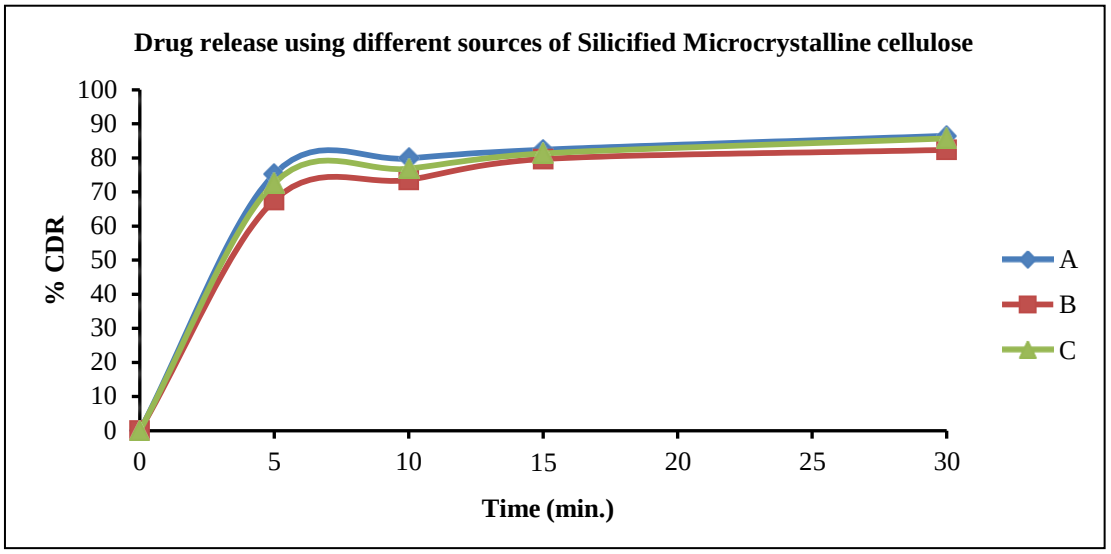

Table 15. Cumulative% drug release for formulations A, B and C.

	Cumulative drug release (CDR) (%)			
Time (min) / Formulation	5	10	15	30
A	75.31	79.87	82.44	86.52
B	67.58	73.56	79.67	82.36
C	72.66	76.87	81.32	85.75

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CONCLUSION

An optimized formulation of IR tablets of Atenolol was prepared by studying design space using QbD approach in this study by direct compression method using Quadratic model of 3^2 full factorial design employed using silicified microcrystalline cellulose, sodium starch glycolate (independent variables) and disintegration time (dependent variable) with excipients magnesium sterate, talc and sweetner. The overlay plot demonstrate that formulation containing Problend 96.026 mg and SSG 9.3 mg was selected to achieve targeted disintegration time using Quadratic model of 3-level full factorial design by Design Expert version 12 Then, three formulations A, B and C were prepared using different samples of SMCC from Gangwal chemicals like Problend, Competitor 1 and Competitor 2 respectively. The results demonstrate that blend prepared from Problend has shown good flow properties than blends prepared using competitor 1 and competitor 2 SMCC. The formulation A shows 86.52% cumulative drug release which contains the drug Atenolol and Problend SMCC. The formulation A was found to be best among all other formulations because it exhibited good wetting time, faster disintegration time and lower% friability when compared to other formulations.

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