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HIGH SHEAR GRANULATION PROCESS: ASSESSING IMPACT OF FORMULATION VARIABLES ON GRANULES AND TABLETS CHARACTERISTICS OF HIGH DRUG LOADING FORMULATION USING DESIGN OF EXPERIMENT METHODOLOGY

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Abstract: High shear wet granulation is a significant component procedure in the pharmaceutical industry. The objective of the study was to investigate the influence of two independent formulation variables; polyvinypyrrolidone (PVP) as a binder (X_1) and croscarmellose sodium (CCS) as a disintegrant (X_2) on the critical quality attributes of acetaminophen granules and their corresponding tablets using design of experiment (DoE) approach. A two factor, three level (3^2) full factorial design has been applied; each variable was investigated at three levels to characterize their strength and interaction. The dried granules have been analyzed for their density, granule size and flowability. Additionally, the produced tablets have been investigated for: breaking force, friability, disintegration time and t_{80} of drug dissolution. The analysis of variance (ANOVA) showed that the two variables had a significant impact ($p < 0.05$) on granules and tablets characteristics, while only the binder concentration influenced the tablets friability. Furthermore, significant interactions ($p < 0.05$) between the two variables, for granules and tablets attributes, were also found. However, variables interaction showed minimal effect for granules flowability as well as tablets friability. Desirability function was carried out to optimize the variables under study to obtain product within the USP limit. It was found that the higher desirability (0.985) could be obtained at the medium level of PVP and low level of CCS. Ultimately, this study supplies the formulator with beneficial tools in selecting the proper level of binder and disintegrant to attain product with desired characteristics.

Keywords: high shear granulation, design of experiment, croscarmellose sodium, polyvinylpyrrolidone, granules, tablets, acetaminophen

High-shear wet granulation (HSWG) – size enlargement process, has been frequently applied in pharmaceutical industry to improve the powder properties like flow and compressibility prior to tableting (1, 2). During HSWG, the enlargement of particle size is attained *via* adding the granulating solution to the powder blend formulation that is being mixed in high shear granulator (3). The powder mixture of tablet formulation chiefly consists of the principal active material, drug, and excipients including the binder, diluent and disintegrant (4). With respect to tablet formulation development, the selection of excipient is crucial particularly for high drug loading formulation (5). Type and amount of excipients during HSWG could influence the physical characteristics of the obtained granules, which in turn, affect the quality attributes of final product, tablet, like disintegration and dissolution (6). Among all the tablet formulation ingredients, binder and disintegrant are usually critical components. On one hand, the binder plays a crucial role in granules formation and is considered a key component in high shear granulation formulation (7). In addition, adding binder to tablet formulation generally

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increases crushing strength and decreases friability of granules and tablets and, at the same time, may increase disintegration time and delay drug release. On the other hand, disintegrant is the driving force behind disintegration of tablets into granules resulting in decreasing the disintegration time and thereby increasing the rate of drug dissolution (8). Therefore, binders and disintegrants have opposing role in tablet formulation.

While a review of the high shear literature revealed that a number of studies examined the impact of the process variables on granules and tablet characteristics. However, it did not reveal any investigations fully examining the interactions between binders and disintegrants in high shear granulation formulation. Despite the critical importance of formulation variables in the pharmaceutical HSWG, a small number of works provided a complete analysis on the effect of binder, disintegrant and their interaction on intermediate, granules and final product, tablets. Therefore, the current research is mainly focused on examination of the impact of binder, disintegrants and their complex interaction on granules and corresponding tablets characteristics of high drug loading formulation using design of experiment approach. Furthermore, the desirability function was applied for the optimization of variables under study to provide formulation of desired attributes.

Designs of experiment (DoE) technique like response surface methodology (RSM) is a helpful tool applied for characterization of pharmaceutical processes through studying the influence of independent variables affecting them and their potential interaction (9).

Acetaminophen was used as a model of principal active drug in the present study, since it demonstrates reduced plastic deformation and poor compactibility. These attributes can result in production of weak compacts giving rise to tablets which are prone to capping even at low compression pressure. Therefore, acetaminophen has been previously chosen as a standard to test the granulation process (10, 11).

EXPERIMENTAL

Materials

Micronized acetaminophen, USP, was provided by Al-Jazera Pharmaceutical Industries Co. (Riyadh, Saudi Arabia). Povidone (Kollidon 30) was purchased from BASF Co. (Ludwigshafen,

Table 1. Variables levels studied in design of experiment.

Coded levels	Polyvinylpyrrolidone level (%)	Croscarmellose sodium level (%)
-1	6	2
0	9	4
1	12	6

-1: factor at low level; 0: factor at medium level; 1: factor at high level.

Table 2. A full matrix of 32 full factorial design for screening of formulation variables.

Experiment code	Polyvinylpyrrolidone level (%)	Croscarmellose sodium level (%)
1	6	2
2	6	4
3	6	6
4	9	2
5	9	4
6	9	6
7	12	2
8	12	4
9	12	6

Germany). Croscarmellose sodium (Ac-Di-Sol) was kindly donated by FMC BioPolymer (Cork, Ireland), and magnesium stearate was obtained from Riedel-de Haën (Seelze, Germany).

Experimental design and methodology

Response surface methodology is advantageous statistical tool that apply to characterize the dependency of response surface on independent variables (12). In the present study, a full factorial design (3^2) was employed to define the impact of polyvinylpyrrolidone (PVP) concentration (X_1) and croscarmellose (CCS) concentration (X_2) as independent formulation variables on granules and tablet attributes of acetaminophen. The levels of each variable are displayed as low level (-1), medium (0) and high level (+1) as seen in Table 1. The full matrix of experiments is shown in Table 2. All batches of experiment were carried out and evaluated in triplicate to decrease the potentiality of error and increase the certainty of results. The statistical analysis of the results was achieved by analysis of variance (ANOVA) using statistical software package (Design Expert 10, USA).

Granules manufacture

Table 3 presents the quantitative composition of the formulation. Granulation experiments were done in a small scale, bottom driven high shear mixer/granulator (Hüttlin mycromix, BOSCH Packaging Technology, Schopfheim, Germany) with a 2L stainless steel vessel equipped with base mounted two blade impeller and vertically mounted a Christmas tree chopper design for de-aggregation of larger agglomerates. The batch size was 500 g in all runs resulting in approximately 50% fill volume. Croscarmellose sodium was layered on the top of acetaminophen and pre-mixed for 2 min. The speed of impeller was retained constant (300 rpm) over pre-blending and process of granulation. The speeds of chopper were kept on high (3000 rpm) at pre-blending and wet massing, while for the phase of wetting, the speed of chopper was fixed to low (1500 rpm). Povidone was dissolved in the granulating liquid and sprayed unto the powder blend using a binary spray nozzle and atomizing air pressure *via* a tube connected to a pre-calibrated pump. The nozzle putted 8 cm above the moving dry powder. After addition of binder solution, the material was wet massed for constant massing time of 3 min. The produced granules were discharged from the granulator bowl and sieved through 2 mm mesh screen. The wet granules were then set as a thin layer (5 mm thickness) and dried in a hot-air convection oven at 60°C to a target loss on drying (LOD) value of 2%. The dried granules were then removed, passed through a 2 mm mesh screen and stored for subsequent evaluation and compression into tablets.

Tablet manufacturing

Acetaminophen granules and magnesium stearate were accurately weighed on an analytical balance and mixed 2 min in Turbula mixer (type S27, Erweka, Apparatebau, Germany). The blend was removed from the mixer and transferred to the hopper of the instrumented RoTap rotary tablet press (kg-pharma, Berlin, Germany). The lubricated blend was compressed into 350 mg tablets using 10 mm standard flat tooling. The produced tablets were collected and stored in tightly high density polyethylene (HDPE) container for subsequent evaluation.

Granules evaluation

Granules size

The average size of granule (n = 3) was measured *via* laser light scattering using Mastersizer 2000, with a Scirocco dry disperser (Malvern Instruments Ltd., UK). The samples (5-6 g) were air dispersed at an inlet air pressure of 1 bar with a 30% feeding rate. Obscuration was continued between 0.6 – 6%.

Granules bulk and tapped density

Granules bulk density was measured using a 50 cm^3 graduated cylinder. The granules were carefully poured into the cylinder up to a particular volume mark (V0). The granules mass (m) was then determined also the bulk density (ρb) was considered in g/cm^3 using Eq. (1).

$$\rho b = m / V0 \quad (1)$$

The tapped density (n = 3) was measured using tap density equipment through exposing the granules in the graduated cylinder to 400 "taps" from a height of approximately 2 cm. It was observed that, in all runs, 400 "taps" were enough to gain a constant occupation volume. The resulting volume after tapping (Vt) was measured to determine the tapped density (ρt) using Eq. (2)

$$\rho t = m / Vt \quad (2)$$

Flowability characteristics

Static angle of repose method was carried out to determine the flowability characteristics on the produced granules for all runs. Static angle of repose measurement was performed by carefully pouring of granules using a dry funnel onto a circular plate to form a conical heap of granules. The funnel was fixed at proximately 4 cm above the heap of gran-

ules. On the test end, the angle among the powder heap surface and the surface plate was calculated *via* measuring pin through aligning it parallel to the granules surface. Static angle of repose was calculated using Eq. (3).

$$\tan(\alpha) = [\text{hight} / (0.5 \times \text{base})] \quad (3)$$

The average of three determinations was considered.

Tablet evaluation

Tablet weight variation and breaking force

An automated tablet tester (ERWEKA Multi-Check 5.1, Germany), was used to determine the weight and breaking force of randomly 20 tablets from each experiment. Results are recorded as the mean ± SD, (n = 20). Tablet breaking force was measured by applying an increasing load across the diameter of the tablet until the tablet breaks. The peak force demand to break the tablet was recorded as the tablet breaking force (13).

Tablet friability

Friability was considered according to USP38-NF33. Twenty tablets were nominated randomly from each batch, weighed and placed into the friabilator (Erweka, TA3R, Heusenstamm, Germany). It was run for 4 min at 25 rpm. After that, the tablets were lightly brushed, weighed in order to measure the tablet weight loss. Tablet friability was determined as a percentage of the weight loss.

Tablet disintegration

Disintegration assessment was performed relating to USP38-NF33 requirements for immediate release tablets. Six tablets from each experiment were placed in a standard USP disintegration apparatus (ERWEKA, Germany) with 900 mL of distilled water as a disintegrating liquid, adjusted at 37 ± 0.5°C. The basket rack assembly was allowed to rise and lower at a constant frequency until the tablets were completely disintegrated and passed through the mesh. The disintegration time of each individual tablet was recorded in minutes. The mean and SD of the six tablets were calculated for each batch.

Tablet dissolution

In vitro drug release was carried out acc. to the USP38-NF33 "Dissolution procedure" for immediate release dosage forms. Six tablets for each experiment were examined using the USP apparatus II method (Erweka, Germany); the paddle was rotated at 50 rpm. Dissolution was done in 900 mL phosphate buffer (pH 5.8 ± 0.05), at 37 ± 0.5°C. Withdrawing of samples was done using 5 mL plastic syringe and replacment with a fresh medium at time interval of 15, 30, 45 and 60 min. The samples were filtered using 0.45 µm membrane filter into clean test tubes. One mL of each sample was removed from the test tube and diluted with phosphate buffer in 50 mL volumetric flask. The diluted

Table 3. Formulation composition details.

Ingredients	% W/W
Intragranule components	
Acetaminophen	81 - 91
Croscarmellose sodium	2, 4, 6
Povidone	6, 9, 12
Distilled water	Q.S.
Extragranular component	
Magnesium stearate	1

Table 4. Results of granules evaluation with coded level of variables and their standard deviation.

Experiment code	X_1 Polyvinylpyrrolidone level	X_2 Croscarmellose sodium level	Y_1 Mean size (µm)	Y_2 Bulk density (g/cm)	Y_3 Tapped density (g/cm)	Y_4 Angle of repose (°)
1	-1	-1	545.31	0.373 ± 0.002	0.513 ± 0.008	36.32 ± 0.13
2	-1	0	575.83	0.375 ± 0.007	0.510 ± 0.004	36.65 ± 0.11
3	-1	1	605.41	0.384 ± 0.002	0.507 ± 0.006	37.45 ± 0.16
4	0	-1	683.91	0.466 ± 0.004	0.530 ± 0.002	29.6 ± 0.12
5	0	0	720.23	0.469 ± 0.006	0.562 ± 0.001	30.00 ± 0.13
6	0	1	760.74	0.491 ± 0.001	0.554 ± 0.003	30.16 ± 0.11
7	1	-1	803.15	0.482 ± 0.006	0.569 ± 0.013	25.97 ± 0.14
8	1	0	845.83	0.507 ± 0.004	0.591 ± 0.001	26.39 ± 0.14
9	1	1	883.61	0.528 ± 0.001	0.573 ± 0.003	26.85 ± 0.12

Table 5. Results of tablets evaluation with coded level of variables and their standard deviation.

Experiment code	X_1 Polyvinylpyrrolidone level	X_2 Croscarmellose sodium level	Y_5 Breaking force (Kp)	Y_6 Friability (g/cm)	Y_7 Disintegration time (g/cm)	Y_8 t_{80} (min)
1	-1	-1	6.12 ± 0.21	2.1 ± 0.01	6.92 ± 1.21	13.46 ± 2.34
2	-1	0	6.26 ± 0.42	1.96 ± 0.07	4.42 ± 0.53	11.21 ± 1.93
3	-1	1	6.83 ± 0.23	2.24 ± 0.03	3.11 ± 0.85	9.78 ± 1.84
4	0	-1	11.32 ± 0.41	0.76 ± 0.02	13.54 ± 1.52	24.76 ± 2.13
5	0	0	11.01 ± 0.11	0.72 ± 0.03	11.24 ± 1.23	21.34 ± 1.77
6	0	1	11.72 ± 0.31	0.74 ± 0.06	9.36 ± 1.43	19.84 ± 1.22
7	1	-1	13.01 ± 0.42	0.33 ± 0.01	17.45 ± 1.84	33.45 ± 2.54
8	1	0	13.41 ± 0.12	0.31 ± 0.03	13.85 ± 1.51	28.84 ± 3.14
9	1	1	13.60 ±0.13	0.28 ± 0.01	10.52 ± 1.26	24.65 ± 2.87

Table 6. Regression analysis data of granules for 3^2 full factorial experimental design, parameters estimate and their p-value.

Variables code	Y_1 Mean size	Y_2 Bulk density	Y_3 Tapped density	Y_4 Angle of repose
intercept	721.81	0.47	0.436	– 29.89
A	134.34 (< 0.0001)	0.064 (< 0.0001)	0.011 (0.0004)	– 5.20 (0.0001)
B	36.23 (< 0.0001)	0.014 (0.003)	-	0.43 (0.011)
AB	5.09 (0.031)	-	-	– 0.063 (0.558)

A: binder level; B: disintegrant level; significant at $p > 0.05$.

samples were then analyzed for acetaminophen concentration using UV spectrophotometer (Shimadzu, UV-1800, Japan) at wavelength 243 nm. Lastly, the produced absorbance was converted into percent drug release using a calibration curve.

RESULTS AND DISCUSSION

Influence of binder and disintegrant on granules characteristics

Granules size

Table 4 lists the results of mean granule size; it was observed that increasing the PVP from 6 to 12% and CCS from 2 to 6% resulted in significant increases in the mean granule size from 545.31 to 883.61 μm. These results are supported by the results of regression analysis, (Table 6). Regression analysis showed that the mean granule size was significantly impacted by PVP concentration ($p < 0.0001$) followed by concentration of CCS ($p < 0.0001$). However, the PVP level had more pronounced effect as shown by the high magnitude of its parameter estimate.

In addition, the two-way interaction between PVP concentration and CCS concentration was found to be statistically significant on their effect on the mean granule size ($p < 0.031$). The positive sign of coefficient estimates is indicating an increase in the mean granule size in response to an increase in the level of PVP and CCS individually or together. A 3D response surface graph was generated to illustrate the influence of PVP and CCs concentration on the mean granule size (Fig. 1).

The magnitudes of mean granule size increase were different depended on the PVP concentration used. The highest percentage increase was found at high PVP concentration (12% w/w) with approximately 32% increase in mean granule size. This is attributed to increasing the concentration of PVP in granulating fluid resulting in formation of highly viscous solution due to its higher hygro-capacity properties; during the granulation process PVP solution was sprayed unto the powder particles that resulted in coating the particle surface with highly viscous material and caused a significant increase in stickiness, which promote the agglomeration process as well as granule growth (14). Also, it was reported that PVP polymer has faster dissolution rate and promotes better granule nucleation process – particularly at low granulating fluid level (15). The previous

results indicate that the binder level has a critical role in granulation process and granule growth.

As shown in Figure 2, the interaction between PVP concentration and CCS concentration suggested that at the highest studied CCS concentration (6% w/w), the effect of the increase in PVP concentration was found maximum at 32% increase. This was due to the additional binding property of CCS used at high concentration.

The predictability of mean granule size by the model was acceptable ($p < 0.0001$). The quadratic model equation that explains the influence of variables on mean granules size can be expressed as the following (variables with $p > 0.05$ were eliminated): Mean granule size = 721.81 + 134.34 binder conc. + 36.23 disintegrant conc. + 5.09 binder conc. × disintegrant conc.

Granules density

As shown in Table 4, the granules bulk and tap density was increased in response to an increase in concentration of PVP and CCS concentration, and ranged from 0.373 to 0.528 and 0.507 to 0.591, respectively. The ANOVA analysis shown in Table 6 indicates that the model is valid with a significant p-value and insignificant lack of fit value, and PVP concentration ($p < 0.0001$) and CCS concentration ($p < 0.003$) have a significant effect on the granules bulk density, with the most significant influential effect affecting granules bulk density being PVP concentration, as shown by the high magnitude of its parameter estimate. The dominant effect of PVP level on granule bulk density could be attributed to: increasing the PVP content resulting in increased viscosity of granulating fluid as well as an increase

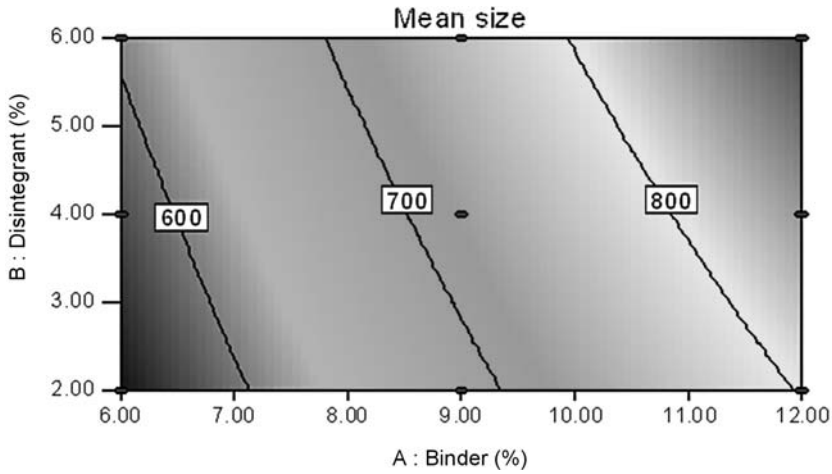

Figure 1. Influence of polyvinylpyrrolidone and croscarmelose sodium concentration on the mean granule size

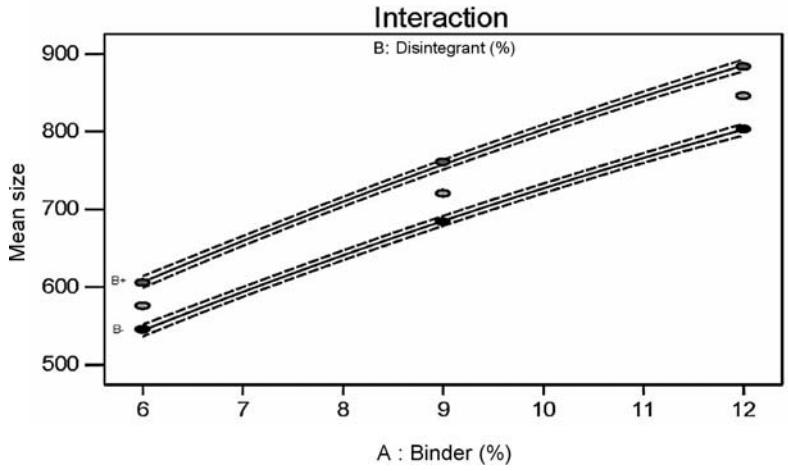

Figure 2. Interaction between polyvinylpyrrolidone and croscarmelose sodium and its impact on the mean granule size

Table 7. Regression analysis data of tablets for 32 full factorial experimental design, parameters estimate and their p-value.

Variables code	Y_5 Breaking force	Y_6 Friability	Y_7 Disintegration time	Y_8 t_{80}
intercept	11.21	0.69	11.17	21.639
A	3.47 (< 0.0001)	- 0.9 (0.0001)	4.56 (0.0001)	8.75 (< 0.0001)
B	0.28 (0.051)	0.012 (0.744)	- 2.49 (0.0008)	- 2.9 (0.0008)
AB	- 0.03 (0.803)	- 0.048 (0.320)	- 0.78 (0.035)	- 1.28 (0.015)

A: binder level; B: disintegrant level; significant at $p < 0.05$.

Table 8. The constraints adopted for the determination of overall desirability.

Variables	Goal	Range (low - high)	Weight	Importance coefficient
Inputs				
Binder conc.	In range	6 - 15%	1	+++
Disintegrant conc.	In range	2 - 6%	1	+++
Outputs				
Breaking force	12 Kp	6.12 - 13.6 Kp	1	+++
Friability	0.5%	0.28 - 2.24%	1	+++
Disintegration time	15 min	3.11 - 17.45 min	1	++++
t_{80}	28 min	9.78 - 33.45 min	1	++++

of the particles consolidation and an increase in the granules density (16). Also it has been reported that increasing the binder content increased the rate and extent of granule consolidation (17).

Moreover, the two-way interaction between PVP concentration and CCS concentration was found to be statistically significant ($p < 0.022$) on their effect on the granules bulk density. All significant terms have positive parameter estimates indicating that an increase in any of the variables individually or together results in an increase in granules density. Figure 3 displays the influence of independent variables on granules density.

As shown in Figure 4, the two way interaction between PVP and CCS concentrations indicates that at the highest level of CCS (6% w/w), the effect of the increase in PVP concentration was found maximum at 27% increase in granules density. This observation suggests that granules density is highly promoted by increasing the binder level.

The predictability of granules bulk density by the quadratic model was acceptable ($p = 0.0002$) and granules bulk density can be described by the following regression equation containing significant independent variables and interactions:

Bulk density = 0.47 + 0.064 binder conc. + 0.014 disintegrant conc. + 8.750E-003 binder conc. × disintegrant conc.

Granules flowability

As shown in Table 4, the angle of repose was declined from 37.45 to 25.97° in response to an increase in PVP and CCS concentrations. Results of regression analysis (Table 6) showed that granules flow was significantly improved by increasing the level of PVP ($p < 0.0001$) and CCS ($p = 0.011$) (Fig. 5). This could be attributed to increased granule size and density as well as reduced the percent fines (18). However, the most influential variable affecting the granules flowability was binder concentration as shown by its high value of its parameter estimate.

The predictability of granules flowability by the quadratic model was acceptable ($p < 0.0001$) and the effect of concentration of PVP and CCS on granules flow was described by the following regression equation containing significant independent variables and interactions:

Angle of repose = 29.89 – 5.2 binder conc. - 0.43 disintegrant conc. – 0.063 binder conc. × disintegrant conc.

Influence of binder and disintegrant on tablets characteristics

Tablets breaking force

The breaking force of compressed tablets ranged from 6.12 to 13.6 Kp (Table 5). As shown in Figure 6, the breaking force was positively correlat-

ed to concentration of PVP suggesting that an increase in the level of PVP in the granulation system resulted in an increase of tablet breaking force. In addition, the ANOVA analysis shown in Table 7 indicates that PVP concentration have a significant impact ($p < 0.0001$) on tablet breaking force. This might be attributed to PVP solution which was sprayed unto the acetaminophen particles. The PVP layer coated on acetaminophen particles will serve as an adhesive layer consequently, upon drying, this will contribute to a stronger bonding resulting in higher tablet breaking force (19). On the other hand, the CCS concentration had minimal effect ($p = 0.052$) on tablets breaking force.

The predictability of granules flowability by the quadratic model was acceptable ($p < 0.0003$) and the effect of concentration of PVP and CCS on granules flow was demonstrated by the following regression equation containing significant independent variables and interactions:

Breaking force = 11.21 – 3.47 binder conc. + 0.28 disintegrant conc. – 0.030 binder conc. × disintegrant conc.

Tablets friability

As shown in Table 5, tablet friability was declined from 2.24 to 0.28%. Fig. 7 demonstrates that, an increase in PVP concentration from 6 to 12% w/w resulted in a significant decrease in tablet friability. In addition, regression of analysis data (Table 7) showed that binder level has significant impact on the tablet friability with very minimal

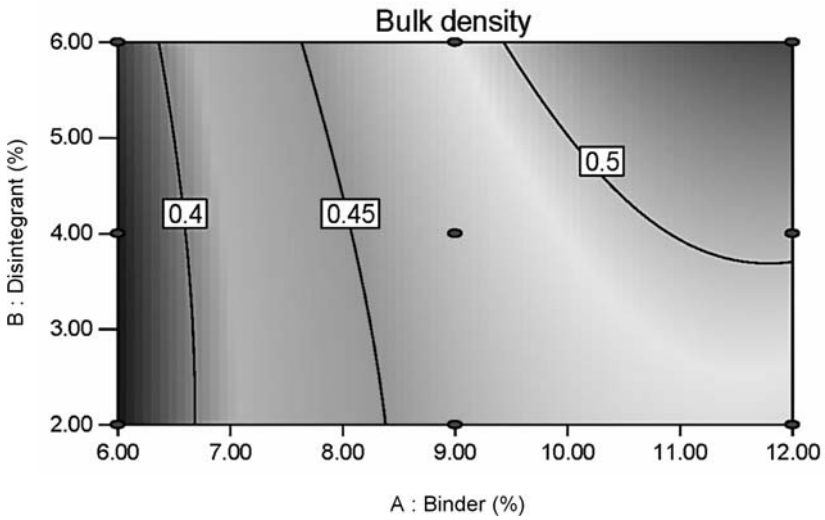

Figure 3. Influence of polyvinylpyrrolidone and croscarmelose sodium concentration on granules bulk density

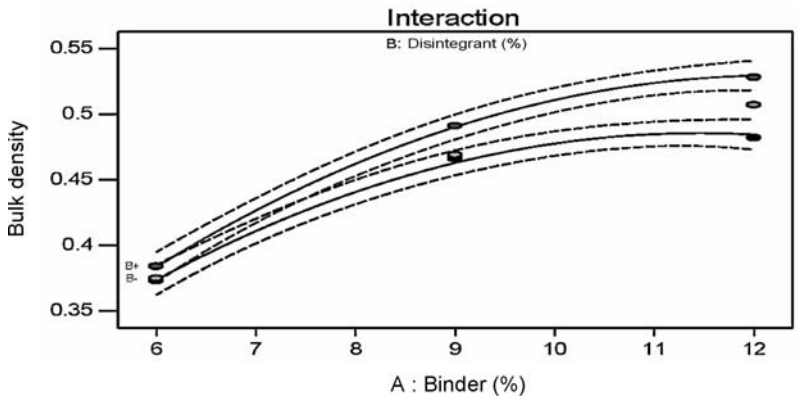

Figure 4. Interaction between polyvinylpyrrolidone and croscarmelose sodium and its impact on the granules bulk density

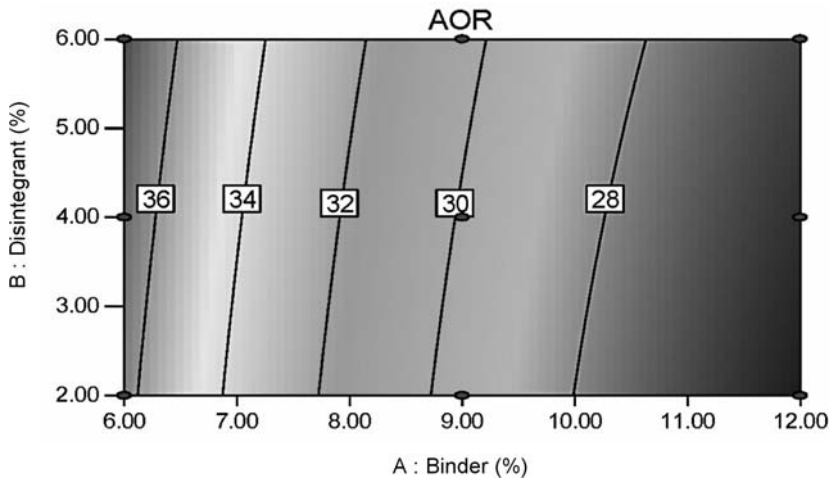

Figure 5. Influence of polyvinylpyrrolidone and croscarmelose sodium concentration on granules flowability (AOR)

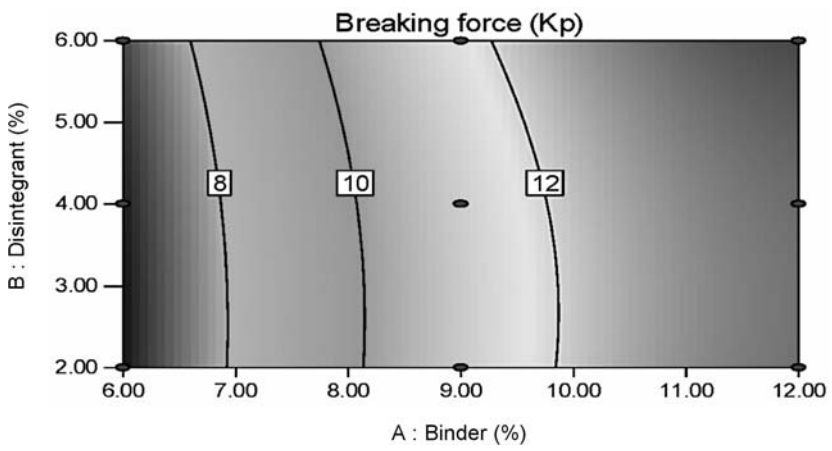

Figure 6. Influence of polyvinylpyrrolidone and croscarmelose sodium concentration on tablets breaking force

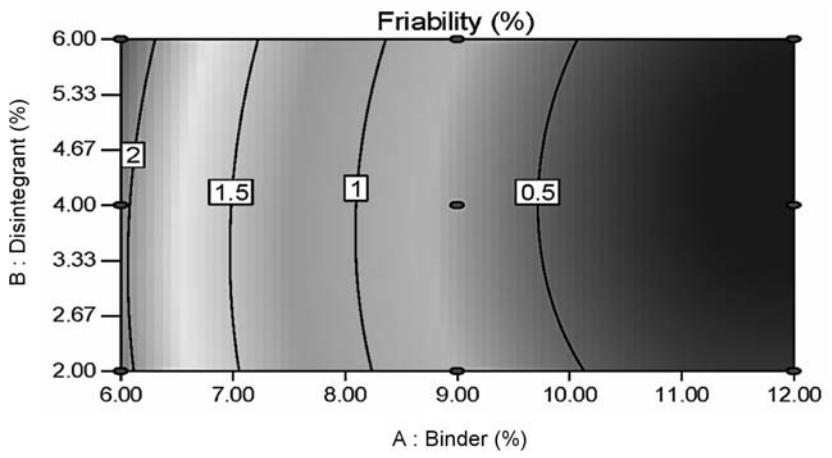

Figure 7. Influence of polyvinylpyrrolidone and croscarmelose sodium concentration on tablets friability

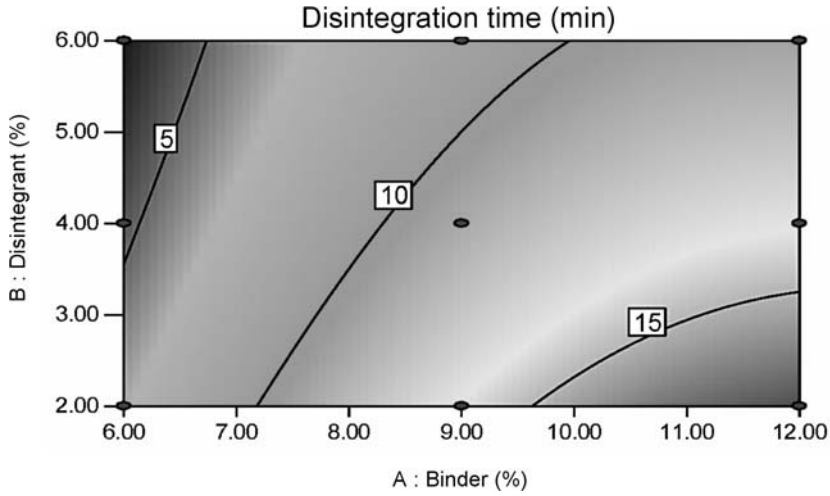

Figure 8. Influence of polyvinylpyrrolidone and croscarmelose sodium concentration on tablets desitegration time

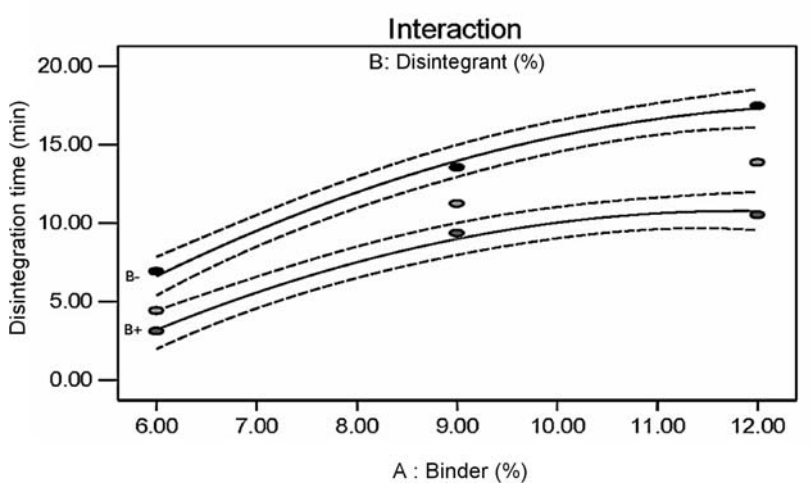

Figure 9. Interaction between polyvinylpyrrolidone and croscarmelose sodium and its impact on tablets disintegration time

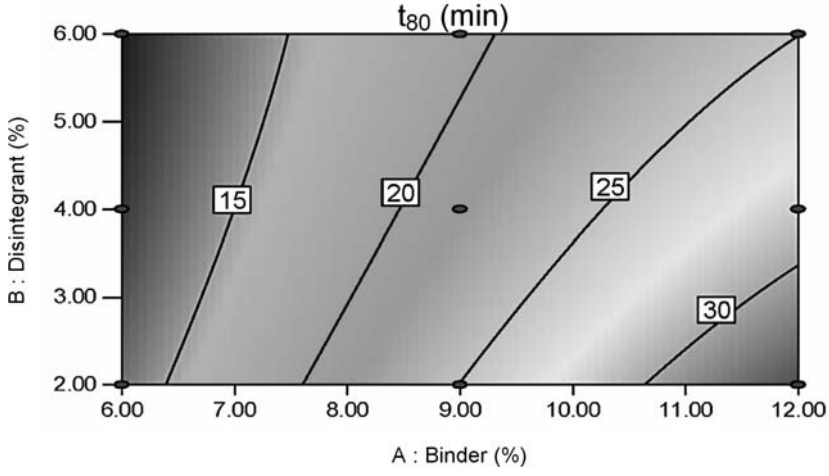

Figure 10. Influence of polyvinylpyrrolidone and croscarmelose sodium concentration on t_{80} of tablets dissolution

effect of disintegrant level. Moreover, the negative sign of the coefficient estimate for the binder level indicates that a high level of binder leads to production of less friable tablets. This could be attributed to the high level of PVP in the granulating solution which could provide better adhesion to acetaminophen particles and formation of highly compressible granules that when compressed into tablets, will give rise to tablets which are less friable (19).

The predictability of tablets friability by the quadratic model was acceptable (p = 0.0007) and the effect of concentration of PVP and CCS on tablets friability was described by the following regression equation containing significant independent variables and interactions:

Friability = 0.69 – 0.9 binder conc. + 0.012 disintegrant conc. – 0.048 binder conc. × disintegrant conc.

Tablets disintegration time

Table 5 presents the results of tablets disintegration time for all runs. Disintegration time ranged from 3.11 to 17.45 min. The results of regression analysis, as shown in Table 7, demonstrated that the level of PVP (p = 0.0001) and CCS (p = 0.0008) has significant effect on tablets disintegration time. However, as shown in Figure 8, the disintegration time was positively correlated with the PVP concentration and negatively with CCS concentration with respect to the sign of their parameter estimate.

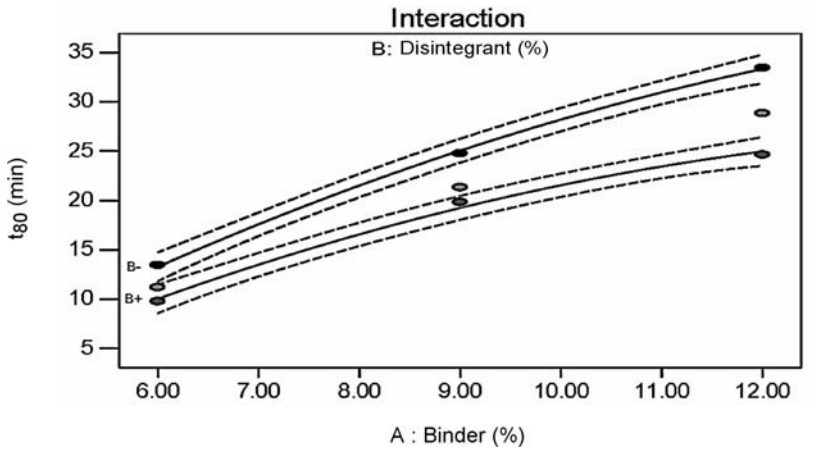

Figure 11. Interaction between polyvinylpyrrolidone and croscarmelose sodium and its impact t_{80} of tablets dissolution

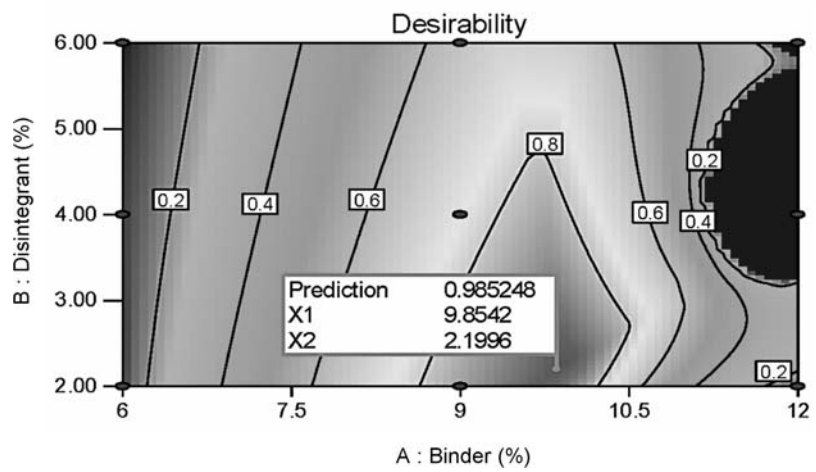

Figure 12. Influence of polyvinylpyrrolidone and croscarmelose sodium concentration on overall desirability

This result indicated that with high PVP level, the disintegration time was significantly delayed whereas an increase in CCS level promotes the tablet disintegration, which resulted in short disintegration time. Furthermore, two-way interaction (p = -0.035) between CCS concentration and PVP concentration indicated that the effect of the CCS concentration depended on the effect of the PVP concentration. As shown in Figure 9, the influence of an increase in CCS concentration on the decrease disintegration time was more pronounced at the high PVP concentration (12% w/w). There was approximately 42% reduction in tablet disintegration time at the high PVP concentration as the CCS concentration increased. The previous results suggested that when the formulator needs to increase the amount of PVP in the formulation, the amount of CCS should also be increased in order to modulate tablet disintegration time to provide tablet with acceptable criteria.

The predictability of tablets disintegration time by the quadratic model was acceptable (p = 0.0006) and the effect of concentration of PVP and CCS on tablets disintegration time was described by the following regression equation containing significant independent variables and interactions:

Disintegration time = 11.7 + 4.56 binder conc.
– 2.49 disintegrant conc. – 2.49 binder conc.
× disintegrant conc.

Tablets dissolution

Table 5 lists the results of t_{80} (time required for 80% of the total drug release) for all runs. As shown in Table 5, an increase in PVP concentration delayed the t_{80} from 13.46 to 33.45 min whereas an increase in CCS concentration facilitated the dissolution process and shorter the t_{80} from 24.65 to 9.78 min. The results of regression analysis, as shown in Table 7, demonstrated that t_{80} was impacted significantly *via* increasing the PVP concentration and CCS. Though, according to the sign of parameter estimates the t_{80} was positively correlated with PVP concentration and negatively with CCS concentration, (Fig. 10).

A significant two-way interaction between PVP concentration and CCS concentration (P = -0.015) indicated that an increase in PVP concentration delayed the t_{80} at low CCS concentration (2% w/w) whereas an increase in CCS concentration shorter the t_{80} at low PVP concentration (6%w/w) (Fig. 11).

According to the previous results of t_{80} we could suggest that when tablet formulation has PVP at 6% or 9% w/w concentration, the recommended concentrations of CCS are 2, 4, 6% w/w in order to provide t_{80} meeting USP requirement for acetaminophen tablets (not more than 30 min) (20). However, when tablet formulation has PVP at 12% w/w, only CCS concentrations at 4 and 6% w/w are recom-

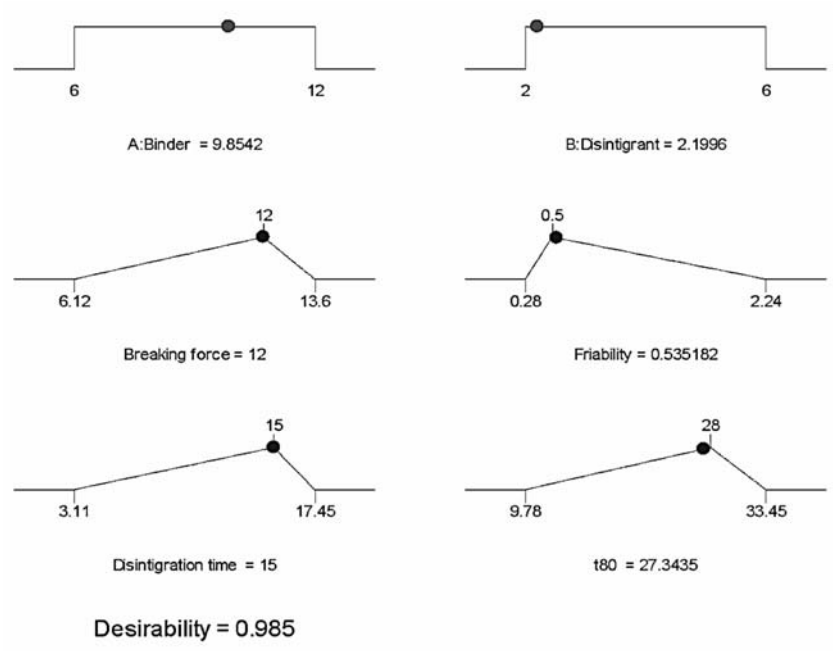

Figure 13. The graphical presentation of the optimal conditions, the predicted responses and corresponding adopted constraints

mended to provide tablets achieving the USP criteria for acetaminophen immediate release tablets.

The predictability of tablets t_{80} by the quadratic model was acceptable (p = 0.0002) and the effect of concentration of PVP and CCS on tablets t_{80} was described by the following regression equation containing significant independent variables and interactions:

$$t_{80} = 21.63 + 8.75 \text{ binder conc.} - 2.9 \text{ disintegrant conc.} - 1.28 \text{ binder conc.} \times \text{disintegrant conc.}$$

Optimization of formulation variables using desirability function

The objective of optimization step is to determine the optimum level of each variable that provide product with desired characteristics. In general, each variable contribute to individual response, upon application of desirability function, all the nominated responses were merged in one overall response called overall desirability (9, 21). In our study, the most desirable outcome is to provide acetaminophen tablets able to achieve the USP criteria for immediate release solid dosage form. In Design Expert software, numerical optimization was carried out to optimize the formulation variables based on the aforementioned responses. Table 8 displays the constraints adopted for the optimization step and determination of overall desirability. Figure 12 showed that the highest value of overall desirability (0.985) could be attained at medium level of PVP (9.85) and low level of CCS (2.19). Graphical presentation of the optimal conditions and the predicted responses and corresponding adopted constraints are shown in Figure 13.

CONCLUSION

This study was generated to screen the acetaminophen granules and tablets manufactured using high-shear granulation. Using design of experiment approach, the influence of formulation variables, binder and disintegrant level on granules and tablets quality attributes was evaluated. The regression analysis data demonstrated that the binder and disintegrant level had significant effect on granules and tablets characteristics. Furthermore, variables interactions were also found to be statistically significant. However, the binder level had the more pronounced effect as shown by its higher parameter estimates for granules and tablets attributes. On the other hand, as it was expected, the binder and disintegrant has opposite impact with respect to their effect on tablets disintegration and dissolution.

Formulation optimization using the desirability function resulted to optimum values of variables at which the goal of tablets production with USP acceptable characteristics could be achieved.

Eventually, this work creates a platform to the formulator in choosing a suitable concentration of binder and disintegrant for development of high drug loading formulation using high-shear granulation methodology.

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Declaration of interest

The authors report no declarations of interest.

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