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# Utilizing mixer torque rheometer in the prediction of optimal wet massing parameters for pellet formulation by extrusion/spheronization

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ABSTRACT

In this study, we aimed to optimize theophylline pellet formulations using a two-factor three-level full-factorial design ($3^2$) by monitoring the concentration of two pellet excipients, polyvinyl pyrrolidone K30 (PVP) binder solution (X1) and the hydrophilic excipient mannitol (X2). Their impact on pellet characteristics (responses) were evaluated. Increasing PVP concentration in the binder solution resulted in an increase in the wet mass torque value. The effect of mannitol, however, was antagonistic. Moreover, the pellet particle size was significantly influenced by the level of mannitol, PVP solution, and quadratic effect of mannitol. Mannitol significantly antagonized the pellet particle size. Furthermore, increased mannitol concentrations significantly enhanced drug dissolution rate from the pellets, whereas PVP concentration in the binder solution significantly reduced the drug dissolution rate. In conclusion, wet granulations can be controlled by monitoring the composition of the binder solution and pellet composition.


## 1. Introduction

Drug dosage form comprised of multiple-units present various advantages compared to single-unit forms. These advantages include steady drug plasma profiles and reduced chance of local adverse reactions (Sandberg et al., 1998). Pellets for use as a multiple-unit pharmaceutical dosage form should be considered owing to their exclusive industrial and clinical benefits. Pellets are free flowing sphere-shaped granules with a narrow size distribution, which normally ranges between 500 and 1500 μm for different pharmaceutical purposes (Chambliss, 1989). Pellets propose several clinical benefits such as reduced irritation to the GIT and reduced risk of adverse reactions owing to the dumping in drug dose (Qazi et al., 2017). In addition, there are technological advantages such as better flow properties, less friable dosage form, narrow particle size distribution, ease of coating, and uniform packing. The *in vitro* release rate of hydrochlorothiazide from Avicel pH 101 pellets was enhanced by the incorporation of polyethylene glycol 400 (PEG-400) and PEG-40 hydrogenated castor oil (Vervaet et al., 1994). Extrusion/spheronization is presently considered as one of the important procedures for the manufacture of pharmaceutical pellets. Pellets with specific attributes could be obtained by monitoring the pellet composition and the extrusion/spheronization conditions. The production of sphere-shaped pellets or granules by extrusion/spheronization procedures has become a more recently recognized method owing to its advantages over the other conventional pellet manufacturing techniques (Patel et al., 2018).

The application of a mixer torque rheometer (MTR) as a true analytical instrument can significantly decrease the quantity of development batches. MTR has been revealed as an outstanding means for the assessment of the pellet wet mass and as a scale-up means for the high-shear granulation processes (Sakr et al., 2012).

MTR optimizes the conditions required for wet massing, in order to attain optimum-quality pellets by extrusion/spheronization. This can be achieved by controlling their wet masses. The effect of microcrystalline cellulose (Avicel®) grade on the pellets produced by extrusion/spheronization has been investigated in previous studies (Alvarez et al., 2002; Soh et al., 2006; Paul et al., 2009; Kuhs et al., 2017). The wet mass torque calculated during the wet massing of eleven Avicel® types was strongly associated with final pellet attributes such as particle size, flowability, and *in vitro* drug release. These studies concluded that MTR can be

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applied to reduce pre-formulation steps related to changes in Avicel® grade. However, the rheological properties of Avicel® blends with the polymeric additives require comprehensive investigation that is focused on optimizing the wet masses of pellets. The volume of the binder solution required for pellet wet massing and the pellet additives require monitoring to optimize the manufacture of pellets during extrusion/spheronization procedures (Paul et al., 2009).

Therefore, the aim of the present study was to explore the effect of pellet wet mass composition on the formulation of pellets containing theophylline, via extrusion and spheronization. We used a two-factor three-level full-factorial design ($3^2$) to optimize theophylline pellet formulations with varying polyvinyl pyrrolidone K30 (PVP) binder solution concentration (X1) and the hydrophilic excipient mannitol (X2).

## 2. Materials and methods

### 2.1. Materials

Theophylline (TN) was purchased from Fluka chemica (Buch, Switzerland). Microcrystalline cellulose (MCC; Avicel® PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). Polyvinyl pyrrolidone (PVP K30) was purchased from Fluka chemica (Buch, Switzerland). Other materials and solvents did not require further purification and were of reagent or analytical grade.

### 2.2. Methods

#### 2.2.1. Experimental design

To optimize pellet formulations, a two-factor three-level full-factorial design ($3^2$) was adopted. The evaluated independent parameters were PVP binder solution (X1) and mannitol (X2) concentrations. All statistical analyses were carried out using Statgraphics Plus, version 5. Statistical models with main, quadratic, and interaction effects were obtained to estimate the impact of the two factors on the pellet wet mass mean line torque in Nm (Y1), mixing time (s) (Y2), pellets particle size (Y3), and drug dissolution rate after 60 min (Y4).

The two independent parameters and their levels, along with the dependent parameters (response) are illustrated in Table 1. The matrix of the factorial design is shown in Table 2. In the matrix, each row recognizes a composition of each run (experiment). An empirical second order polynomial model was provided by this design, where each dependent parameter, experimental response (Y), can be represented by a quadratic equation of the response surface:

$$Y = B0 + B1X1 + B2X2 + B3X1X2 + B4X1^2 + B5X2^2$$

where B0 is an intercept and B1–B5 are the regression coefficients.

**Table 1**
Variables in $3^2$ full factorial design.

| Independent variable, Factor | | | |
|---|---|---|---|
| | Low (−1) | Middle (0) | High (1) |
| X1: PVP K30 solution (%) | 0.5 | 1.25 | 2.0 |
| X2: Mannitol (%) | 0.0 | 10.0 | 20.0 |
| **Dependent variable, Response** | | | |
| Y1: Meanline torque (Nm) | | | |
| Y2: Mixing time (s) | | | |
| Y3: Particle size (μm) | | | |
| Y4: Dissolution efficiency after 15 min, $DE_{15}$ (%) | | | |

**Table 2**
Composition of pellet formulations.

| Formula | PVP solution (%) | Mannitol (%) | Avicel pH 101 (%) | Drug (%) |
|---|---|---|---|---|
| F 1 | 0.5 | 0 | 90 | 10 |
| F 2 | 1.25 | 20 | 70 | 10 |
| F 3 | 2 | 10 | 80 | 10 |
| F 4 | 2 | 20 | 70 | 10 |
| F 5 | 2 | 0 | 90 | 10 |
| F 6 | 1.25 | 0 | 90 | 10 |
| F 7 | 0.5 | 20 | 70 | 10 |
| F 8 | 0.5 | 10 | 80 | 10 |
| F 9 | 1.25 | 10 | 80 | 10 |

#### 2.2.2. Pellet wet mass characterization using a mixer torque rheometer

The properties of the pellet wet mass were characterized to obtain the maximum peak torque (to determine the optimum binder ratio) and the optimum mixing time by using a mixer torque rheometer. The mixer torque rheometer consisted of a stainless-steel bowl (135-ml capacity) fitted with two mixing blades that operate at a speed range between 15 and 160 rpm (MTR-3, Caleva, Dorset, England). A powder weight of 15–30 g was adequate to cover the MTR mixing blades. The wet mass torque was calculated on the mixer bowl with the aid of a torque arm linked from the main body of the mixer to a calibrated load transducer. Wet mass was measured by operating the MTR at a speed of 50 rpm. Data acquisition and analysis were carried out using a data acquisition system and software package.

In the Turbula mixer (Erweka type S27, Apparatebau, Germany), 15 g of solid pellet excipients were mixed for 5 min, and placed in the MTR bowl. Two ml of binder solution was added to the bowl via multiple additions over 10 intervals for wet massing. Each wet massing interval involved a mixing period of 1 min and 20 s torque data logging (gathering) time with the MTR. Wet mass consistency represented by the mean line torque, Nm, was measured during the wet massing procedures (Ibrahim et al., 2015).

To determine the mixing time, 15 g of the sample was added to the bowl of the mix torque rheometer and the volume of the binder solution (as obtained from the previous experiment of the maximum peak torque study) added. The equipment was then adjusted for a mixing time of 15 min.

#### 2.2.3. Extrusion/spheronization procedures

While manufacturing pellets loaded with 10% w/w TN, water containing different PVP concentrations was used as the binder solution. The volume of the binder solution for each wet massing cycle was selected based on the maximum value of wet mass torque calculated by the mix rheometer. Different pellet formulas were prepared based on the $3^2$ full-factorial design, and their compositions are listed in Table 1. Pellet excipients and TN were blended in a turbula mixer for 5 min. The powder blend was then transferred to the MTR bowl and wetted with a suitable volume of the binder solution as obtained from the maximum peak torque studies. The powder was left for mixing with the binder solution in the MTR bowl to obtain the optimum mixing time reported in previous studies. The resultant wet mass was then ejected through a screen pore size of 1 mmØ (Mini Screw Extruder, Model MSE1014, Caleva, Dorset, England) at an extrusion speed of 90 rpm (Mahrous et al., 2010). Consequently, the produced extrudates were spheronized at a speed of 800 rpm, for 5–7 min, using a revolving plate of even cross-hatch geometry (Spheronizer Model 120, Caleva, Dorset, England). Finally, the pellets obtained were dried at 60–70 °C for 5 h on a tray placed in a hot oven.

#### 2.2.4. Drug content

The drug content in the manufactured pellet formulations was assessed spectrophotometrically in triplicate. A specific weight of

**Table 3**
Properties of pellet formulations.

| Formula | Mean line torque (Nm) | Binder ratio (mL/g) | Mixing time (s) | Particle size (μm) | % DE after 15 min |
|---|---|---|---|---|---|
| 1 | 1.07 | 1.33 | 670 | 1368 | 78.02 |
| 2 | 0.74 | 1.00 | 530 | 975 | 83.44 |
| 3 | 1.21 | 0.667 | 680 | 1254 | 71.23 |
| 4 | 0.89 | 0.667 | 540 | 1100 | 77.34 |
| 5 | 1.35 | 1.00 | 870 | 1487 | 54.27 |
| 6 | 1.24 | 1.00 | 720 | 1421 | 67.84 |
| 7 | 0.37 | 0.667 | 420 | 784 | 97.01 |
| 8 | 0.50 | 1.00 | 480 | 875 | 84.51 |
| 9 | 0.84 | 0.667 | 520 | 987 | 81.41 |

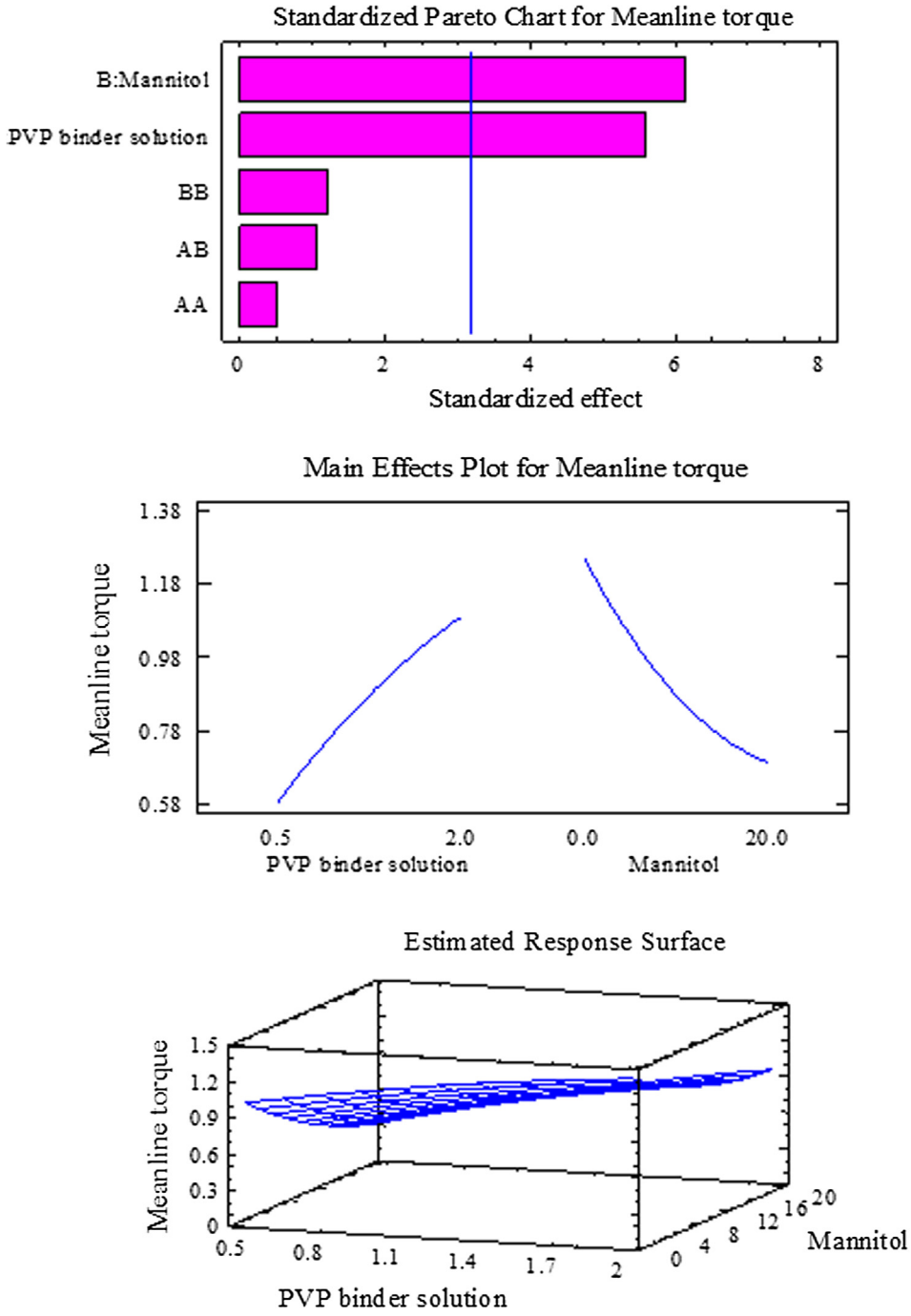


**Fig. 1.** Standardized Pareto chart (A), Main effects (B) and 3D contour response surface plot estimating the effect of PVP concentration (X1) and mannitol (X2) on the mean line torque value of pellet wet masses.

the pellet formula was pulverized, from which approximately 25 mg was suspended in 250 mL of phosphate buffer (pH = 6.8). The dispersion was sonicated for 10 min, and filtered through a filter with a 0.45-μm pore diameter (Sartorius, Göttingen, Germany). The filtrate was then measured spectrophotometrically at 272 nm (UV-2800 spectrophotometer, Labomed Inc., USA) to determine TN content (Ibrahim et al., 2015).

*2.2.5. Particle size*

The size distribution of the pellet formulations was recorded by laser light diffraction (Mastersizer Scirocco 2000, Malvern Instruments, Grovewood Road, U.K.). In brief, approximately 500 mg of formula was introduced into the micro feeder of the sample. All pellet formulas were measured 5–7 times, and the average results were considered. The values of d(0.1), d(0.5), and d(0.9) were utilized to describe the pellet size distribution. The size distribution span value was used to describe the size distribution of pellet formulas. A small span value designates a narrow distribution of particle size. Span value was computed using the following equation (Ibrahim, 2013):

$$\text{Span} = (D90 - D10)/D50$$

*2.2.6. In vitro dissolution studies*

The *in vitro* dissolution of TN from the pellet formulations was performed based on the USP dissolution basket method (apparatus 1) using a dissolution tester (LOGAN Instrument Corp, Somerset, NJ, USA). A weight of the pellet formula, equivalent to 50 mg of the drug, was placed in the dissolution basket immersed in 500 mL of phosphate buffer at pH 6.8. The equipment was operated at 50 rpm, and the temperature was maintained at 37 ± 0.5 °C. Drug *in vitro* dissolution studies were performed up to 1 h in triplicates. Samples were withdrawn at pre-determined intervals, and absorbance was recorded at 272 nm. The amount of dissolved TN was calculated as a function of time.

## 3. Results and discussion

### 3.1. Effect of independent parameters

*3.1.1. Effect on pellet wet mass*

Pellet wet mass is one of the most crucial parameters that should be optimized before pellet manufacturing. The impact of

**Table 4a**
Analysis of variance for the mean line torque of pellet wet masses.

| Source | Sum of squares | DF | F-ratio | P value |
|---|---|---|---|---|
| X1: PVP K30 solution | 0.381528 | 1 | 31.38 | 0.0112 |
| X2: Mannitol | 0.457056 | 1 | 37.60 | 0.0087 |
| $X1^2$ | 0.0032805 | 1 | 0.27 | 0.6393 |
| X1X2 | 0.013924 | 1 | 1.15 | 0.3630 |
| $X2^2$ | 0.01805 | 1 | 1.48 | 0.3101 |

R-squared = 95.99.
**Equation:** Meanline torque = 0.814222 + 0.437556X1 binder solution − 0.0564333X2 − $0.072X1^2$ + .00786667X1X2 + $0.00095X2^2$.

**Table 4b**
Analysis of variance for the mixing time for the pellet wet masses.

| Source | Sum of squares | DF | F-ratio | P value |
|---|---|---|---|---|
| X1: PVP K30 solution | 45066.7 | 1 | 24.73 | 0.0156 |
| X2: Mannitol | 98816.7 | 1 | 54.23 | 0.0052 |
| $X1^2$ | 800.0 | 1 | 0.44 | 0.5550 |
| X1X2 | 1600.0 | 1 | 0.88 | 0.4179 |
| $X2^2$ | 8450.0 | 1 | 4.64 | 0.1203 |

R-squared = 96.56.
**Equation:** Mixing time = 617.778 + 53.3333X1 − 22.5X2 + $35.5556X1^2$ − 2.66667X1X2 + $0.65X2^2$.

**Table 4c**
Analysis of variance for the mixing time for the pellet size.

| Source | Sum of squares | DF | F-ratio | P value |
|---|---|---|---|---|
| X1: PVP K30 solution | 0.110704 | 1 | 25.66 | 0.0149 |
| X2: Mannitol | 0.334648 | 1 | 77.57 | 0.0031 |
| $X1^2$ | 0.000566722 | 1 | 0.13 | 0.7410 |
| X1X2 | 0.00970225 | 1 | 2.25 | 0.2307 |
| $X2^2$ | 0.0455014 | 1 | 10.55 | 0.0476 |

R-squared = 96.56.
**Equation:** Particle size = 1.31656 + 0.0406296X1 − 0.0619917X2 + $0.0299259X1^2$ + 0.00656667X1X2 + $0.00150833X2^2$.

**Table 4d**
Analysis of variance for the mixing time for the $\%DE_{15}$.

| Source | Sum of squares | DF | F-ratio | P value |
|---|---|---|---|---|
| X1: PVP K30 solution | 535.739 | 1 | 17.30 | 0.0253 |
| X2: Mannitol | 554.189 | 1 | 17.90 | 0.0242 |
| $X1^2$ | 16.0631 | 1 | 0.52 | 0.5234 |
| X1X2 | 4.15344 | 1 | 0.13 | 0.7385 |
| $X2^2$ | 51.2882 | 1 | 1.66 | 0.2884 |

R-squared = 96.56.
**Equation:** $\%DE_{15}$ = 78.173 − 1.36222X1 + 1.80403X2 − $5.03822X1^2$ + 0.135867X1X2 − $0.05064X2^2$.

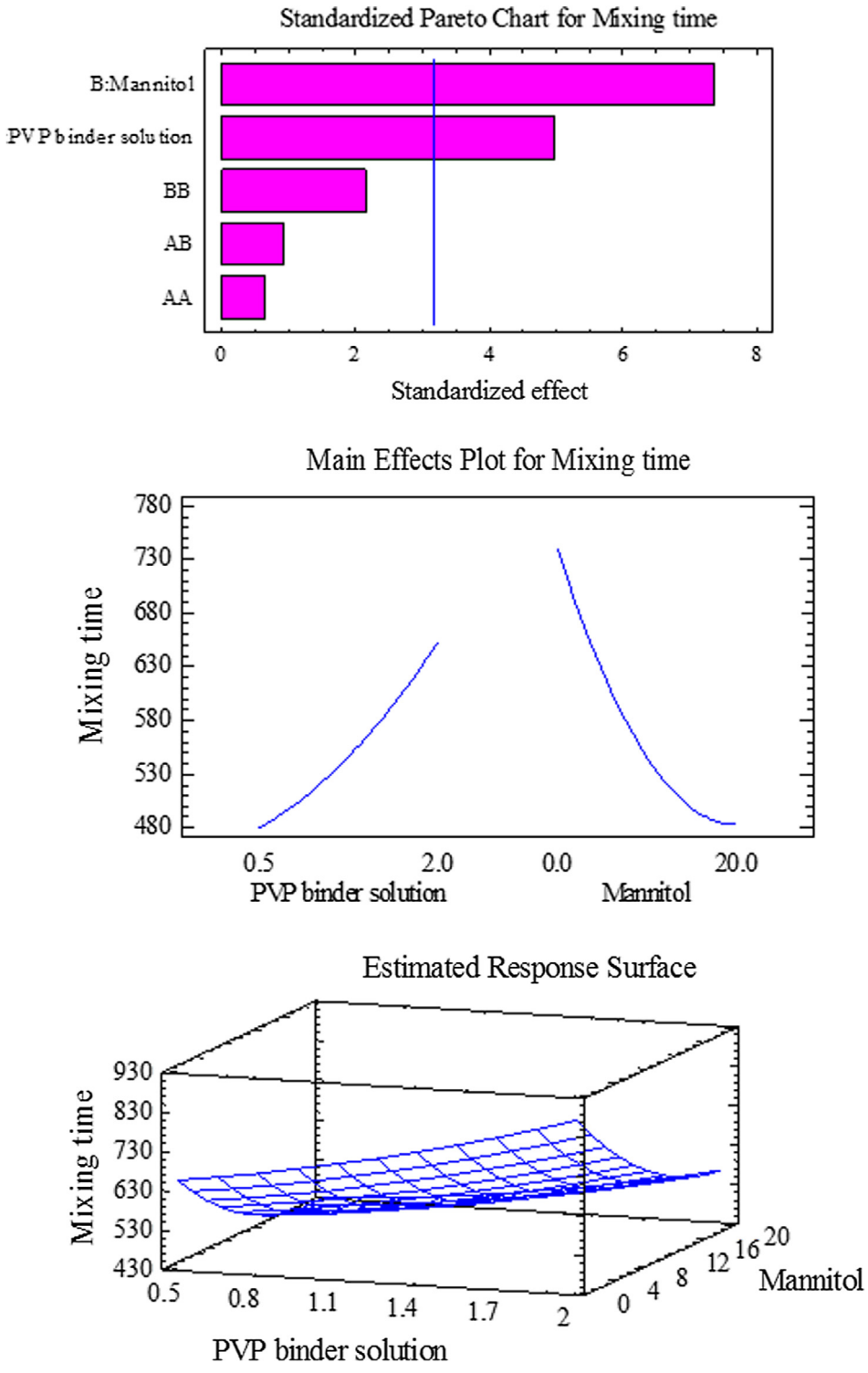


**Fig. 2.** Standardized Pareto chart (A), Main effects (B) and 3D contour response surface plot estimating the effect of PVP concentration (X1) and mannitol (X2) on the mixing time of pellet wet masses.

different concentrations of the binder solution PVP K 30 (X1) (0.5, 1.25 and 2% w/v) and the pellet excipient mannitol (X2) (0, 10 and 20%) on pellet wet mass (represented by mean line torque; Nm) is shown in Table 3 and Fig. 1. It was found that mannitol (X2) significantly affected the wet mass torque ($p = 0.0087$) and the PVP solution (X1) in which the recorded p value was 0.0112. This is illustrated using ANOVA as shown in Table 4a. As indicated from the main effect data (Fig. 1b), the effect of X1 on the pellet wet mass was agonistic. Thus, increasing PVP concentration in the binder solution results in an increase in the wet mass torque value, as

shown in Table 4b and 4c. In contrast, the effect of mannitol was antagonistic against the torque of the pellet wet masses, and the pellet wet mass torque reached its lowest value (0.37 Nm) when 20% of mannitol was used along with the lowest concentration of PVP concentration. This is reflected in F8, Table 3. Moreover, the quadratic effects ($X1^2$ and $X2^2$) as well as the interactive effect on pellet wet mass torque were not significant, as their recorded p values were higher than 0.05 in all cases (Table 4a). The antagonistic effect of mannitol on the wet mass consistency (especially when lower PVP concentration was used as the binder solution) may be due to the hydrophilic nature of mannitol (Wang and Friess, 2017). This hydrophilic nature allows good wetting of the powder bed with the binder solution, which results in a subsequent reduction in the wet mass consistency (torque).

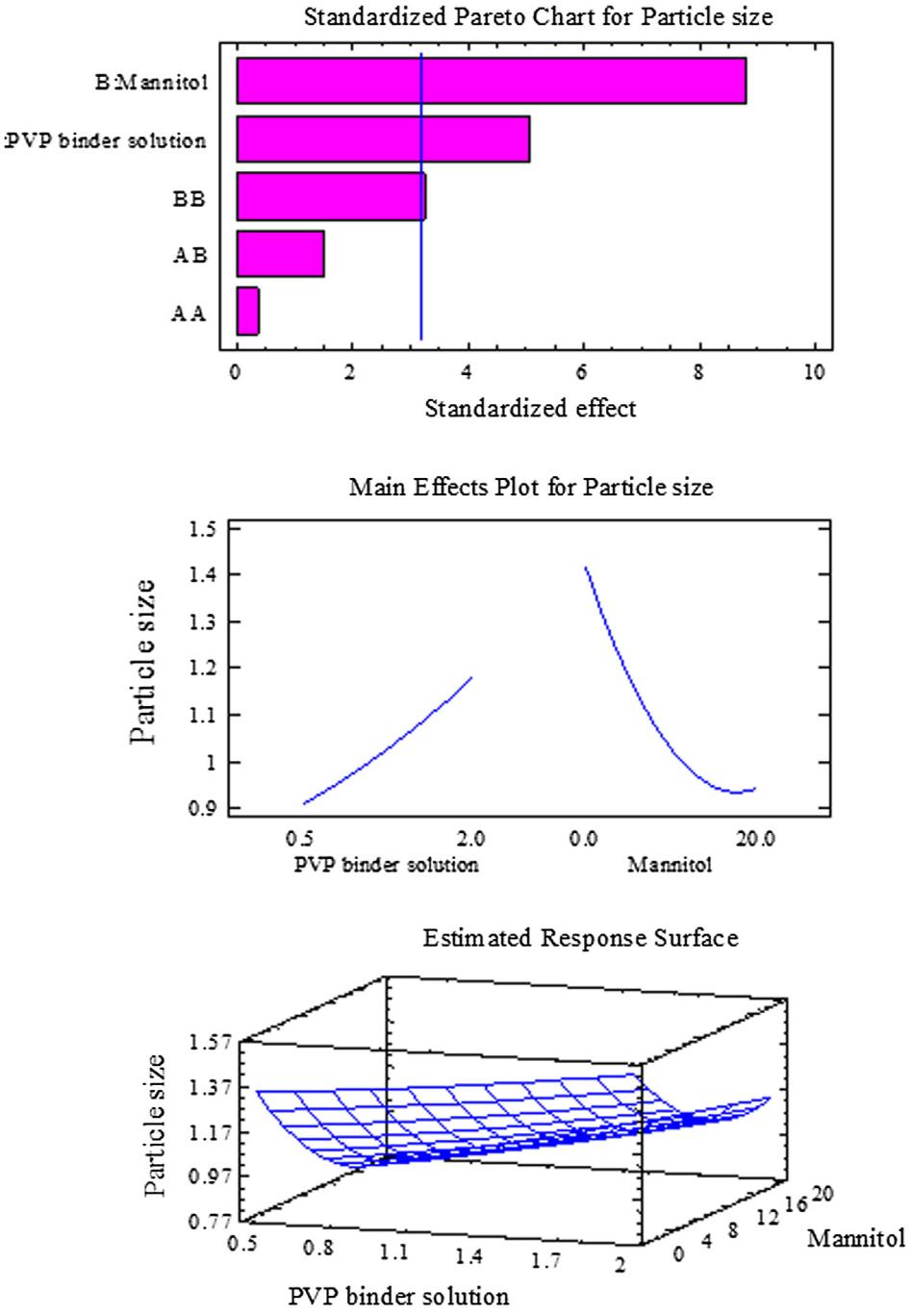


**Fig. 3.** Standardized Pareto chart (A), Main effects (B) and 3D contour response surface plot estimating the effect of PVP concentration (X1) and mannitol (X2) on the pellets' sizes.

*3.1.2. Effect on pellet mixing time*

The effects of the binder solution (X1) and mannitol (X2) on the mixing time of the pellet powder masses are shown in Table 3 and Fig. 2. Mannitol concentration significantly (0.0052) affected the mixing time of the powder mixture antagonistically, whereas the PVP solution significantly (0.01546) influenced the mixing time agonistically. In contrast, the quadratic effects ($X1^2$ and $X2^2$) and the interactive effect of the powder mixing time were not significant ($p > 0.05$). At high mannitol levels and low PVP concentration, a rapid wetting of the powder with the binder solution prevailed. A short mixing time was therefore required. When higher PVP concentrations are used in the absence of mannitol (F5 and F6), the wet massing procedure was attained after long mixing times (870 s and 720 s, respectively). In addition, these formulations

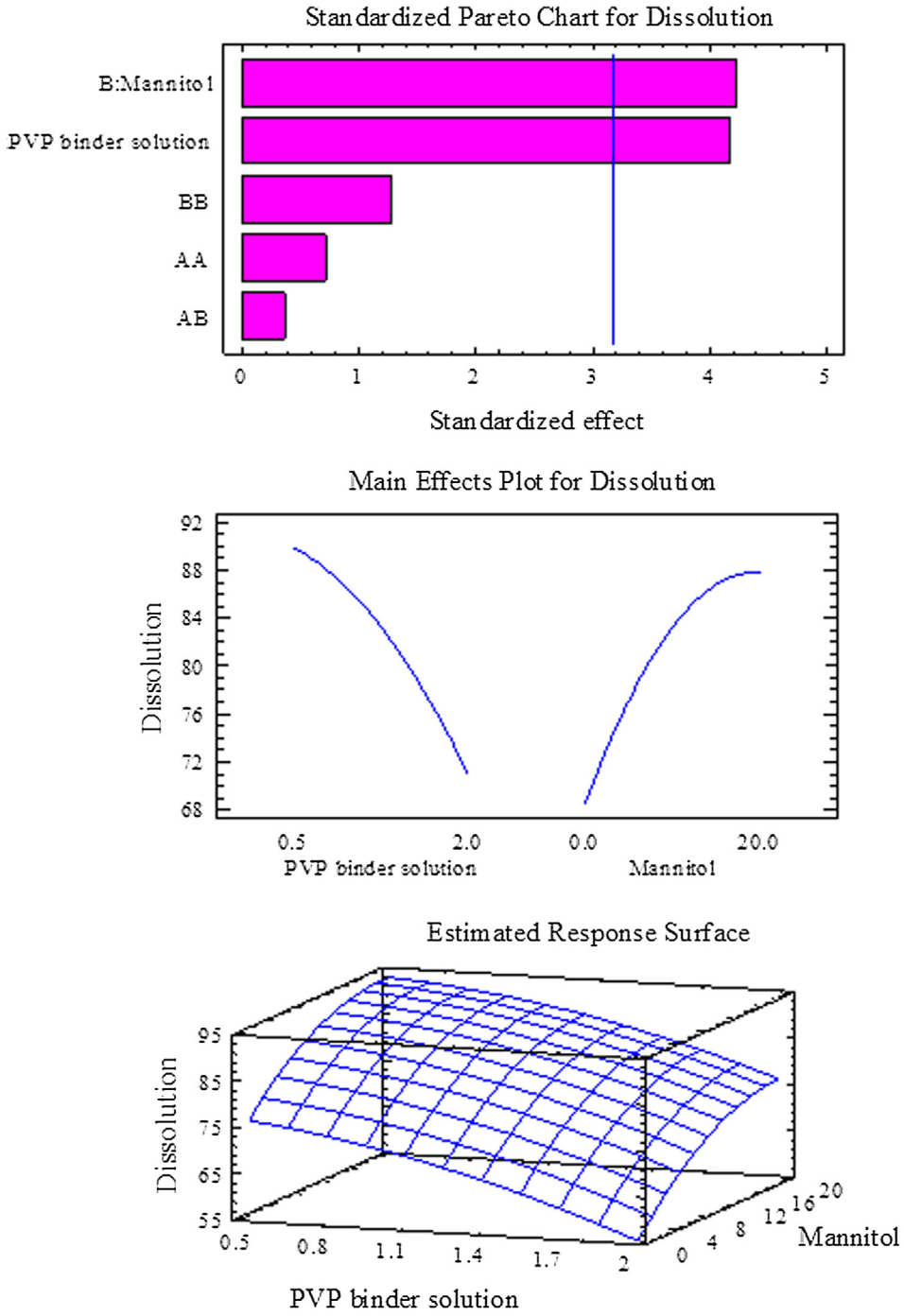


**Fig. 4.** Standardized Pareto chart (A), Main effects (B) and 3D contour response surface plot estimating the effect of PVP concentration (X1) and mannitol (X2) on the dissolution efficiency of theophylline after 15 min ($\%DE_{15}$) from pellet formulations.

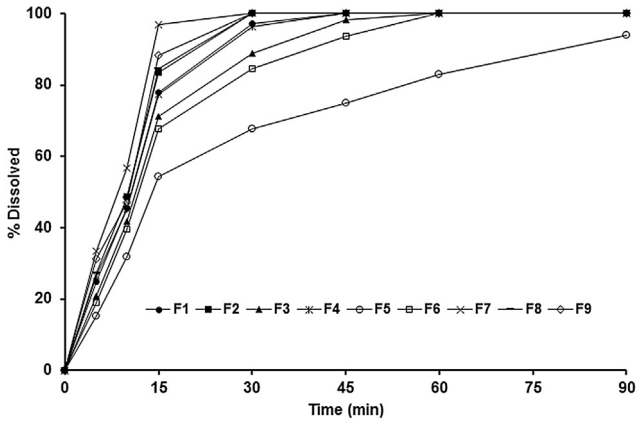


**Fig. 5.** Dissolution patterns of theophylline from pellet formulations.

showed the highest mean line torque values (1.35 Nm and 1.24 Nm, respectively, Table 3). This may be a result of the passage of the wet mass through funicular and pendular phases (before maximum torque), resulting in the formulations occurring slowly (Ibrahim et al., 2015).

### 3.1.3. Effect on pellet size

The effect of the independent variables X1 and X2 on the particle size of the pellets produced by extrusion/spheronization procedures is tabulated in Tables 3 and 4c, and illustrated in Fig. 3. The pellet particle size was significantly influenced by mannitol levels ($p = 0.00310$), the PVP binder solution ($p = 0.0149$), and the quadratic effect of mannitol (p-0.0476) as shown in the Pareto chart and the ANOVA table. The pellet content of X2 (mannitol), individual or quadratic ($X2^2$), was found to significantly antagonize the pellet particle size, i.e., small particle sizes were obtained with increasing levels of mannitol, especially at lower PVP solution concentrations. The interactive effect of X1X2 on the pellets size was very slight and insignificant, the p value obtained from ANOVA was higher than 0.05. The smallest pellet sizes were observed in F7 and F8 (784 and 875 μm, respectively), where 20% of mannitol was used with 0.5% PVP solution (F7) and 10% of mannitol was used with 0.5% PVP solution (F8). It is worthy to mention that these formulations exhibited very low peak torque values (0.37 and 0.50 Nm, respectively) for their wet masses. The results obtained by Mahrous et al. (2010) revealed that increasing PEG 4000 concentration (hydrophilic excipient) in the pellet wet mass on the expense of Avicel®, a wet mass of minimum consistency (mean line torque), resulted in a value comparable to the mean line torque recorded when a similar weight of PVP or HPMC is used. Low wet mass consistency resulted in the easy extrusion and production of smoother surfaces of the pellet formula and small pellet sizes. Law and Deasy (Law and Deasy, 1997) showed that the incorporation of hydrophilic polymers with Avicel® resulted in the production of more spherical pellets with smoother surfaces and smaller sizes.

### 3.1.4. Effect on % $DE_{15}$

Dissolution of the drug from the pellet formulations in phosphate buffer (pH 6.8) was calculated, and the data represent the percentage of dissolution efficiency after 15 min (% $DE_{15}$). The effects of PVP solution (X1) and mannitol (X2) on the DE were almost similar; however, their effect was in opposite directions. Mannitol concentration significantly (0.0242) enhanced the drug dissolution rate from the pellets, whereas PVP concentration in the binder solution significantly reduced the drug dissolution rate (0.0253) (Table 4d and Fig. 4). The calculated sum of squares was 535.74 and 554.2 for the effects of PVP and mannitol, respectively. Moreover, the interactive effect of X1X2 on the % $DE_{15}$ was insignificant (p value obtained from ANOVA was higher than 0.05). The drug exhibited higher dissolution efficiency values after 15 min from the pellet formulations F7 and F8 (97.01 and 84.51, respectively), which contained high mannitol levels and the lowest PVP concentration. The response surface plot in Fig. 4D also shows that increasing the PVP level in the binder solution resulted in a remarkable reduction in the %$DE_{15}$ value at lower mannitol levels.

The presence of a hydrophilic excipient (mannitol) with Avicel® in the pellet formulation resulted in a lower wet mass peak torque (consistency). This resulted in the production of small pellet sizes and, in turn, enhanced the drug dissolution rate from such formulations. Ibrahim (Ibrahim, 2013) reported that a lower peak torque value of the pellet wet masses results in smooth surface textures. In addition, he showed that an inverse relationship exists between the mean line torque and the dissolution behavior (Fig. 5). Moreover, Law and Deasy (Law and Deasy, 1997) reported that mixing different hydrophilic excipients with Avicel® (1:19) facilitates the extrusion/spheronization process and increases indomethacin dissolution *in vitro*.

### 3.2. Optimized pellet formulation

To validate the regression equations or model, a check point of X1 = 0.5% and X2 = 18.4% was selected. The composition of the optimized pellet formula was estimated based on previous data. The effects of X1 and X2 on the responses were evaluated, and the predicted responses on the optimized pellet formulation were calculated based on the following desirability criteria: minimum mean line torque, minimum mixing time, minimum particle size, and maximum % $DE_{15}$ (Table 5). Optimization was carried out using multiple response optimization. Optimum concentrations were verified using the contour plots of all responses. The predicted and observed values of mean line torque, mixing time, pellet size, and %$DE_{15}$ for the previously mentioned check point were in strict correlation with the model-predicted response values. At this optimum level, the optimized pellet formula showed a mean line torque of 0.371 Nm (predicted) and 0.389 ± 0.04 Nm (observed), mixing time of 434.86 s (predicted) and 465.0 ± 9.8 s (observed),

**Table 5**
Composition of the optimized pellet formula, the desirability of responses and their observed and predicted values.

| Optimized formula composition | Response | | | |
|---|---|---|---|---|
| | Type | Desirability | Predicted | Observed |
| PVP solution (X1): 0.5%<br>Mannitol (X2): 18.40% | Y1: Mean line torque (Nm)<br>Y2: Mixing time (s)<br>Y3: Particle size (μm)<br>Y4: $DE_{15}$ (%) | Minimum<br>Minimum<br>Minimum<br>Maximum | 0.371<br>434.86<br>774.10<br>93.53 | 0.389 ± 0.04<br>465.0 ± 9.8<br>758.5 ± 15.84<br>95.74 ± 4.52 |

pellet size of 774.10 μm (predicted) and 758.5 ± 15.84 μm (observed), and $\%DE_{15}$ values of 93.53% (predicted) and 95.74 ± 4.52% (observed).

## 4. Conclusion

The present study indicated that the process of pellet formulation or even wet granulation can be controlled by monitoring the composition of the binder solution and the composition of the formulation itself. Therefore, the measurement of wet mass properties such as binder ratio and wet mass peak torque (by using mix torque rheometry) will play a crucial role in optimizing pellets or wet granules on an industrial scale.

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## References

Alvarez, L., Concheiro, A., Gómez-Amoza, J.L., Souto, C., Martínez-Pacheco, R., 2002. Effect of microcrystalline cellulose grade and process variables on pellets prepared by extrusion–spheronization. Drug Dev. Ind. Pharm. 28, 451–456.

Chambliss, W.G., 1989. Pharmaceutical Pelletization Technology. In: Ghebre-Sellassie I. Marcel Dekker, New York, pp. 15–38.

Ibrahim, M.A., 2013. Formulation and evaluation of mefenamic acid sustained release matrix pellets. Acta Pharm. 63, 85–98.

Ibrahim, M.A., Mahrous, G.M., Shazly, G.A., Radwan, A.A., 2015. Formulation of theophylline-loaded pellets based on chitosan: Powder wet mass characterization. Lat. Am. J. Pharm. 34, 797–802.

Kuhs, M., Moore, J., Kollamaram, G., Walker, G., Croker, D., 2017. Predicting optimal wet granulation parameters for extrusion-spheronisation of pharmaceutical pellets using a mixer torque rheometer. Int. J. Pharm. 517, 19–24.

Law, M.F.L., Deasy, P.B., 1997. Use of canonical and other analyses for the optimization of an extrusion-spheronization process for indomethacin. Int. J. Pharm. 146, 1–9.

Mahrous, G.M., Ibarhim, M.A., El-Badry, M., Al-Anazi, F.K., 2010. Indomethacin sustained release pellets prepared by extrusion/spheronization. J. Drug Deliv. Sci. Technol. 20, 119–125.

Patel, S., Patel, N., Misra, M., 2018. Controlled-release domperidone pellets compressed into fast disintegrating tablets forming a multiple-unit pellet system (MUPS). J. Drug Deliv. Sci. Technol. 45, 220–229.

Paul, K.E., Fridrun, P., Michael, N.J., 2009. The rheological properties of modified microcrystalline cellulose containing high levels of model drugs. J. Pharm. Sci. 98, 2160–2169.

Qazi, F., Shoaib, M.H., Yousuf, R.I., Nasiri, M.I., Ahmed, K., Ahmad, M., 2017. Lipids bearing extruded-spheronized pellets for extended release of poorly solubleantiemetic agent—Meclizine HCl. Lipids Health Dis. 16, 75–91.

Sakr, W.F., Ibrahim, M.A., Alanazi, F.K., Sakr, A.A., 2012. Upgrading wet granulation monitoring from hand squeeze test to mixing torque rheometry. Saudi Pharm. J. 20, 9–19.

Sandberg, A., Ragnarsson, G., Jonsson, U.E., Sjogren, J., 1998. Design of a new multiple-unit controlled-release formulation of metoprolol–metoprolol CR. Eur. J Clin. Pharmacol. 33, S3–S7.

Soh, J.L.P., Liew, C.V., Heng, P.W.S., 2006. Torque rheological parameters to predict pellet quality in extrusion-spheronization. Int. J. Pharm. 315, 99–109.

Vervaet, C., Baert, L., Remon, J.P., 1994. Enhancement of *in vitro* drug release by using polyethylene glycol400 and PEG-40 hydrogenated castor oil in pellets made by extrusion/spheronisation. Int. J. Pharm. 8, 207–221.

Wang, B., Friess, W., 2017. Formation of mannitol core microparticles for sustained release with lipid coating in a mini fluid bed system. Eur. J. Pharm. Biopharm. 120, 126–132.