BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902022e20544

Article

Optimization of the Extragranular Excipient Composition of Paracetamol Tablet formulation using the Quality by Design Approach

Yonni Eshovo Apeji[1]*, Naima Avosuahi Ariko[1], Olubunmi Jumoke Olayemi[2], Adeniji Kehinde Olowosulu[1], Avosuahi Rukayat Oyi[1]

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria, [2]Department of Pharmaceutical Technology and Raw Materials Development, National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria

The purpose of this study is to optimize the composition of extragranular excipients (EGE) and mixing time of granules with EGE of paracetamol tablet formulation using Design of Experiments (DoE) approach. The effect of the composition of EGE and the mixing time of granules with EGE on granule and tableting properties of paracetamol tablet formulation was investigated using a combined model of mixture and process factors (Design-Expert 12). A total of 18 tablet formulations were manufactured by wet granulation using varying compositions of EGE and varying mixing time. Granule and tablet properties of each formulation were evaluated as response variables for the design, data generated were fitted into models and analysed to generate a design space that was used for optimization studies. The proposed EGE composition as predicted by the design was confirmed and validated after preparation and evaluation of the granule and tablet properties. The optimized composition for the EGE that yielded granules and tablets of desirable characteristics was found to be maize starch (5 %), talc (4.9 %) and magnesium stearate (0.1 %) with a mixing time of 2 min. The tablets produced with the optimized composition had better mechanical strength and disintegration time than the formulation prepared using an existing formula of maize starch (7.8 %), talc (2 %) and magnesium stearate (0.2 %) that were obtained using the One Variable at a Time (OVAT) approach. This study confirmed the relevance of quality by design in development of pharmaceutical formulations.

Keywords: Optimization. Design of experiment. Extragranular excipients. Granule properties. Tablet properties.

INTRODUCTION

Solid dosage forms broadly encompass tablet and capsule formulations. It has been estimated that solid dosage forms constitute 90 % of all dosage forms used to provide systemic administration of therapeutic agents (Zhang *et al.,* 2017) thereby portraying their importance in drug delivery. However, tablets are the most widely used because they are convenient to carry. They are relatively stable and can be produced in diverse forms (Patel, Kaushal, Bansal, 2006).

Tablets are produced by combining the Active Pharmaceutical Ingredients (API) and excipients in a series of processes involving mixing, granulation and compression (Andrews, 2007). These processes involve the experimentation of several formulation and process variables to arrive at a product of desirable quality. Hence, to obtain tablets of acceptable quality, it is necessary to optimize the formulation and process variables of tablet production. However, formulation development of tablets cannot be adequately accomplished using the traditional "trial and error" approach of OVAT (Bodea, Leucuta, 1997). This

***Correspondence:** Y. E. Apeji. Department of Pharmaceutics and Industrial Pharmacy. Faculty of Pharmaceutical Sciences. Ahmadu Bello University. Zaria-810271, Nigeria. Phone: +234-8052622947. E-mail: yehonathanapeji@gmail.com. ORCID: https://orcid.org/0000-0002-3116-7570

calls for the adoption of rational, systematized, efficient strategies using "Quality by Design" (Singh *et al.,* 2011).

Quality by Design (QbD) is a systematic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. This concept according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8 Guidance states that "quality cannot be tested into products, i.e. quality should be built in by design (ICH, 2009). QbD identifies characteristics that are critical to quality from the perspective of the patient, which translates them into the attributes that the drug product should possess and establishes how the critical process parameters can be varied to produce a drug product with the desired characteristics consistently. In order to achieve this, the relationship between formulation, manufacturing process variables (including drug substances and excipient attributes and process parameters) and product characteristics must be established. In like manner, the sources of variability must be identified. This knowledge is used to implement a flexible and robust manufacturing process that is adaptable and can produce a consistent product over time (Yu, 2008).

Several studies have been carried out to optimize tablet formulation development with respect to the intragranular excipients (diluent, binder, disintegrant) (Miyamoto *et al.,* 1998; Alebiowu, Itiola, 2003; Rodríguez-amado *et al.,* 2015; Khampeng, Otsuka, Peerapattana, 2019). However, there is little or no information on the optimization of the EGE added to the granules prior to compression into tablets. Therefore, the purpose of this study is to optimize the extragranular excipient composition of paracetamol tablet formulation using the QbD approach.

Extragranular excipients are the fraction of excipients added after granulation and before compression or tableting. They serve as disintegrants, glidants and lubricants (Debotton, Dahan, 2017). These excipients affect the performance of tablets *in vivo* and in specific tablet parameters such as crushing strength and disintegration time etc. Therefore, it is necessary to optimise the addition of the EGE to any tablet formulation for maximum efficacy.

The most common disintegrant used in conventional tablets is starch, with potato and corn starches being the most common types used. The typical concentration range of starch used as disintegrants in tablet formulations is up to 10 %w/w. Starch particles swell once in contact with water. This swelling can subsequently disrupt the tablet (Desai, Liew, Heng, 2016). Disintegrants can be mixed with other ingredients before granulation. Thus, they are incorporated within the granules (intragranular addition). They can also be mixed with the dried granules before compression (extragranular addition). The latter procedure contributes to the effective disintegration of the tablet into smaller fragments. Disintegrants can therefore, be incorporated both intragranularly and extragranularly (Roy, Hasan, Kumar, 2011; Odeku, Akinwande, 2012).

The role of the glidant as an extragranular excipient is to improve the flowability of the granules (Apeji, Olowosulu, 2020). They are often added to a granulation before compression into tablets to ensure that the granules flow sufficiently from the hopper during high-speed production. Traditionally, talc has been used as a glidant in tablet formulations and in concentrations of about 1 – 2 % by weight (Jadhav *et al.,* 2013).

The function of the lubricant is to ensure that tablet formation and ejection can occur with low friction between the granules and the die wall. High friction during tableting can cause a series of problems, including capping or even fragmentation of tablets during ejection and vertical scratches on tablet edges which may lead to abrupt halt in production (Kalies, Heinrich, Leopold, 2020). Lubricants are thus included in almost all tablet formulations. Whereas magnesium stearate has become the most widely used lubricant owing to its superior lubricant properties, the stearic acid salts are also used at low concentrations of < 1% by weight (Wang, Wen, Desai, 2010).

Apart from reducing friction, lubricants may cause undesirable changes in the properties of the tablet. The presence of a lubricant in a powder mix is thought to interfere with the bonding between the powder particles during compaction, thus reducing tablet strength (Almaya, Aburub, 2008). Since many of the lubricants are hydrophobic, tablet disintegration and dissolution are often retarded by the addition of a

lubricant (Perrault, Bertrand, Chaouki, 2011). These adverse effects are strongly related to the amount of lubricant present and a minimum amount (0.25 – 1 %) is recommended for tablet formulations. The method of incorporation of a lubricant, the total mixing time and the mixing intensity are process variables that should be considered in order to achieve a good quality formulation. This can be achieved by using Design of Experiment as a tool to implement QbD.

Design of Experiment (DoE) is a structured and organized method usually adopted or used to determine the relationship among factors that influence the outcome of a process. It is an optimization technique meant for products and/or processes developed to evaluate all potential factors simultaneously, systematically, and speedily. Its implementation invariably encompasses the use of statistical experimental designs, generation of mathematical equations and graphic outcomes. Thus, it portrays a complete picture of variation of response(s) as a function of the factor(s) (Singh *et al.,* 2011).

In the present study, the effect of varying the EGE composition and mixing time on the granule and tableting properties of paracetamol tablet formulation was investigated using a combined model of mixture–process order generated by the Design of Experiment approach. This was compared with a reference formulation whose extragranular excipient composition was obtained by the trial and error (OVAT) approach.

MATERIAL AND METHODS

Material

Paracetamol, lactose, talc, magnesium stearate (BDH Chemicals Ltd Poole, England), maize Starch (Burgoyne Burbidge & Co. Mumbai, India), Sodium hydroxide pellets (Qualikems Laboratory Reagent, India), Potassium dihydrogen phosphate (Guangdong Guanghua Sci-Tech Co. Ltd, China), Distilled Water.

Design of Experiments

The effect of EGE composition and their mixing time on the granule and tableting properties of paracetamol tablets was investigated using a combined model of mixture and process factors (Design-Expert version 12, Stat-Ease Inc., Minneapolis, MN 55413, USA). The design generated using the Design-Expert (version 12, Stat-Ease Inc., Minneapolis, MN 55413, USA) was based on the input factor variables of maize starch (5-8 %), talc (0.1 – 4.9 %) and magnesium stearate (0.1 – 4.9 %) as EGE and mixing time (2 & 5 min) as a process variable. Paracetamol granules were prepared according to the formula given in Table I and each formulation of paracetamol granules was blended with a mix of EGE according to the composition and mixing time given in Table II to obtain 18 possible formulations. The granules were evaluated for angle of repose, Carr's index and Hausner ratio as response variables for the design before tableting. Paracetamol tablets were produced by compressing granules on the Single Punch Tablet Press (Type EKO, Erweka, Apparatebau-G.m.b.H, Germany). The tablets were kept for 24 h to allow for elastic recovery and the parameters of crushing strength (CS) and Disintegration Time (DT) were evaluated as response variables for the design. The data obtained from the response variables were fitted into models and analysed statistically using ANOVA. The model generated for each response was validated and used to predict the optimal composition of the EGE and mixing time.

TABLE I - Formula for preparing paracetamol granules and tablets

	Quantities	
Ingredients	**1 tablet**	**100 tablets**
Paracetamol (77 %)	0.5	50
Lactose (5 %)	0.0325	3.25
Maize starch (5 %)	0.0325	3.25
Maize starch paste (3 %)	0.0195	1.95
Extragranular excipient (10 %)	0.065	6.5
Total (g)	0.65	65

TABLE II - Input variables and their varied levels

Run	MS (%)	TLC (%)	MST (%)	MT (min)
1	7.25	0.925	1.825	2
2	8	0.1	1.9	5
3	5.75	3.325	0.925	5
4	5.75	0.925	3.325	2
5	6.5	1.75	1.75	2
6	5	0.1	4.9	5
7	5	4.9	0.1	2
8	7.25	1.825	0.925	5
9	8	1.9	0.1	5
10	5	0.1	4.9	2
11	5	4.9	0.1	5
12	5.75	0.925	3.325	5
13	7.25	1.825	0.925	2
14	7.25	0.925	1.825	5
15	8	0.1	1.9	2
16	6.5	1.75	1.75	5
17	8	1.9	0.1	2
18	5.75	3.325	0.925	2

MS – Maize starch, TLC – Talc, MST – Magnesium stearate, MT – Mixing time

Optimization of EGE composition and mixing time

The composition of EGE was optimized using the numerical optimisation technique (Design Expert). Optimal combinations of EGE were predicted using set targets for the responses employed in the design and the solution obtained was selected based on the desirability function (Surajit, Susanta, 2018). The composition of EGE as predicted by Design Expert ver. 12 was validated and confirmed by preparing a trial formulation of paracetamol tablet while incorporating the predicted formula of EGE. The angle of repose of the granules, the crushing strength and disintegration time of the tablets were evaluated as observed responses and compared to the predicted responses.

Formulation of paracetamol tablets using the optimized composition of EGE

Paracetamol tablets were prepared by wet granulation according to the formula given in Table III. Appropriate quantities of paracetamol powder were mixed with corresponding quantities of lactose and maize starch by geometric dilution in a mortar using a pestle.

Maize starch paste was used to bind the powder mix together and the wet mass was screened through a 1.5 mm mesh sieve while the granules formed were dried in the hot-air oven (Gallenkamp, England) at 40 ^{o}C for 15 min. The granules were further screened through 1.0 mm mesh sieve and dried again in the oven at 40 ^{o}C for 2 h. The dried granules were mixed with the EGE in a cube mixer for 2 min and compressed into tablets (650 mg target weight) on a Single Punch Tablet Press at a compression force of 9 KN. The tablets were kept for 24 h to allow for elastic recovery and the properties of the tablets evaluated afterwards. A reference formulation containing paracetamol (Table III) was prepared using a conventional formula of EGE obtained by OVAT approach.

TABLE III - Formula for preparing paracetamol tablets incorporating the optimised extragranular excipient composition

	Formulations	
Ingredients	**I**	**II**
Paracetamol (77 %)	500	500
Lactose (5 %)	32.5	32.5
MS (5 %)	32.5	32.5
MS paste (3 %)	19.5	19.5
Extragranular excipients		
MS (5, 7.8 %)	32.5	50.7
TLC (4.9, 2 %)	31.85	13
MST (0.1, 0.2 %)	0.65	1.3
Total (mg)	**650**	**650**

MS – Maize starch, TLC – Talc, MST – Magnesium stearate

Evaluation of granule and tablet properties

Particle Size Analysis

Mean granule size of paracetamol granules was determined using the sieving method (Allen, Popovich, Ansel, 2005). A set of mechanical sieves (710, 500, 250, 150, 90, 75 µm) were arranged in descending order in the Endecott's test sieve shaker. Paracetamol granules were poured unto the first sieve and the nest of sieves was agitated for 10 min. The weight of granules retained on each sieve was determined and the mean granule size was calculated using Equation 1.

$$Mean\ Granule\ Size = \frac{\Sigma(\%\ weight\ of\ powder\ retained\ on\ each\ sieve \times sieve\ size)}{100} \quad \text{Eq.1}$$

The angle of Repose (°)

The angle of repose of paracetamol granules was determined using the fixed funnel method as described by Choudhari *et al.* (2018). The granules were poured at an angle of 45° through a glass funnel suspended at a height above the horizontal surface. The height (h) and radius (r) of the cone-shaped heap of the powder formed as a result of the fall was measured. The angle of repose was calculated using Equation 2. A mean of three determinations was recorded as the final angle of repose.

$$Tan\ \theta = \frac{h}{r} \quad \text{Eq. 2}$$

Bulk and Tapped Densities

Bulk and tapped densities of paracetamol granules were determined by pouring 20 g of the granules into a 100 mL measuring cylinder. The initial volume occupied by the granules was recorded as bulk volume (V_B). The cylinder was tapped until the volume of granules became constant and was recorded as tapped volume (V_T). Bulk and tapped densities were calculated using Equations 3 & 4 respectively.

$$BD = \frac{weight\ of\ powder}{bulk\ volume(V_B)} \quad \text{Eq. 3}$$

$$TD = \frac{weight\ of\ powder}{tapped\ volume(V_T)} \quad \text{Eq. 4}$$

Carr's index and Hausner ratio, which are indicators of flow and compressibility were calculated using Equations 5 & 6 respectively. A mean of three replicates was recorded for each parameter.

$$CI = \frac{TD - BD}{TD} \times 100\ \% \quad \text{Eq. 5}$$

$$HR = \frac{TD}{BD} \quad \text{Eq. 6}$$

Moisture content determination

The moisture content of paracetamol granules was determined by gravimetric method (Ohwoavworhua, Adelakun, 2010). A sample of granules (2 g) was dried to constant weight at 105 °C in a hot air oven (Gallenkamp, England). The % moisture content was after that calculated using Equation 7

$$\%\ moisture\ content = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100\ \% \quad \text{Eq. 7}$$

Uniformity of weight

The weight of twenty tablets sampled randomly from each formulation was determined individually. The mean weight and standard deviation for each formulation was reported.

Tablet thickness

The thickness of five tablets from each formulation was measured using the digital vernier calliper (Moore and Wright, England). A mean of five replicates was reported with standard deviation.

Crushing strength determination

The breaking force required to crush the tablet when force is applied diametrically on the tablet was measured using the Monsanto hardness tester. A mean of five determinations was recorded with the standard deviation.

Tablet Disintegration

The time taken for tablets from each formulation to disintegrate was evaluated using the Erweka disintegration tester (Type ZT3, Erweka Apparatebau-G.m.b.H Heusenstamm, Germany). Six tablets were selected at random and placed in cylindrical tubes containing perforated discs at the base of the tube. The cylindrical tube setup was immersed in distilled water at 37 °C ± 0.5. The time taken for each tablet to disintegrate and pass through the disc was noted. The disintegration time was reported as a mean of six replicates with standard deviation for each formulation.

Tablet Friability

The collective weight of 20 randomly selected tablets was obtained and the tablets were placed in the Friabilator (Type TA3R, Erweka Apparatebau-G.m.b.H Heusenstamm, Germany) where it was allowed to rotate at 25 rpm for 4 min. Afterwards, the tablets were retrieved, dusted, and their final weight was obtained. Tablet friability was then calculated using Equation 8 below

$$\%\ friability\ = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100\ \% \quad \text{Eq. 8}$$

Calibration curve for paracetamol

Phosphate buffer solution (pH 5.8) was prepared by dissolving potassium dihydrogen phosphate (32.66 g) in distilled water (1200 mL). Sodium hydroxide: NaOH (1.6 g) pellets was also dissolved in distilled water (200 mL). Potassium dihydrogen phosphate solution (1000 mL) was mixed with NaOH solution (75 mL) in a volumetric flask, and the volume made up to 4000 mL with distilled water. Serial dilutions of a paracetamol solution in phosphate buffer (pH 5.8) were prepared by dissolving 50 mg of paracetamol powder in 500 mL of the buffer solution to give a 0.1 mg/mL stock solution. 1mL of this solution was measured out and diluted to 100 mL with the buffer solution giving a 1µg/mL concentration. From this stock solution, 1 mL, 2 mL, 3 mL, up to 7 mL respectively was taken and diluted to 10 mL in different test tubes respectively. The wavelength of maximum absorption for paracetamol was obtained by scanning a sample dilution from 200 – 400 nm using a UV spectrophotometer and it was found to be 244 nm. The absorbance of the prepared dilutions was then determined at 244 nm obtained from a scan of a sample dilution using the Spectrophotometer (Shimadzu corporation, USA)

A calibration curve of absorbance against concentration was obtained and the straight-line equation of the plot was resolved as $y = 0.1925x + 0.1349$.

In vitro Dissolution Studies

In vitro dissolution studies was performed using a USP dissolution apparatus Type I (Type DT, Erweka - Apparatebau - G.m.b.H, Germany), using the basket method at 100 rpm. One tablet was placed in the basket and lowered into the beaker containing 900 mL of phosphate buffer solution (pH 5.8) maintained at 37 ± 0.5 °C. 5 mL samples were withdrawn intermittently at specified times (5, 10, 20, 30, 45, and 60 mins) and replaced with an equal volume of the dissolution medium after each withdrawal. The samples withdrawn were suitably diluted with the buffer solution, and the absorbance read at 244 nm using the UV spectrophotometer. The percentage of drug dissolved was calculated using the equation of the calibration curve and a plot of percentage drug released against time was drawn. This test was conducted in triplicate.

RESULTS AND DISCUSSION

Design of Experiments

The granule and tablet properties of the 18 preliminary formulations screened for optimization are given in Table IV. The angle of repose of the preliminary

granule formulations were between 27 ° and 34.8 °, Carr's index and Hausner ratio were between 11.8 % and 22.8 % and 1.13 and 1.30 respectively. Crushing strength of their tablet formulations was between 111 N and 138 N while disintegration time was between 1.02 min and 15 min. The variation in granule and tablet properties across formulations can be attributed to the composition of EGE although all the granule formulations exhibited excellent flow properties irrespective of the composition of EGE.

However, it was observed that formulations containing concentrations of TLC greater than 3 % gave rise to granules with slightly lower values of angle of repose (Runs 7, 11 & 18). This can be attributed to the glidant action of TLC which enhances the flow of powders and granules by reducing interparticulate friction and the degree of cohesion between particulates (Jadhav *et al.,* 2013). The action of MST, on the other hand, was found to increase the angle of repose at concentrations higher than that of TLC (Runs 5, 10 & 12). The effect of MS did not appear to exert much significance on the granule properties possibly because of the narrow range of concentration employed (5 – 8 %) and its traditional role as a disintegrant in tablet formulation (Hartesi *et al.,* 2016). Its effect was readily observed on tablet properties where lower values of DT were obtained with increasing concentrations of MS in the presence of low concentrations of MST (Runs 8 & 9). MST was found to exert a pronounced effect on tablet properties by prolonging the DT with increasing concentration (Runs 10 & 12). The effect of concentration of MST in the presence of different mixing time was found to influence the DT (Runs 2 & 9). A lower mixing time gave rise to faster DT while longer mixing time (5 min) prolonged the DT. This can be attributed to the hydrophobic nature of MST. As a lubricant, MST forms a layer or film on the surface of the granules thereby impairing the uptake of water during disintegration (Perrault, Bertrand, Chaouki, 2011). When mixing time of the granules with the lubricant is increased, a higher degree of coating is achieved which further delays the rate at which water is taken up into the tablet matrix, thereby prolonging disintegration time. Hence, the mixing time is a critical process parameter that should be carefully considered when lubricating granules for tablet formation.

TABLE IV - Granule and tablet parameters of the preliminary formulations

Run	AR (°)	CI (%)	HR	CS (N)	DT (min)
1	27.00 ± 1.23	21.40 ± 0.98	1.27 ± 0.03	130 ± 1.50	3.00-±-0.25
2	30.80 ± 1.19	22.80 ± 0.86	1.30 ± 0.01	126 ± 2.80	10.11-±-0.54
3	31.50 ± 1.23	18.50 ± 1.10	1.23 ± 0.02	130 ± 2.00	7.08-±-0.36
4	32.90 ± 1.18	16.70 ± 0.88	1.20 ± 0.03	130 ± 2.00	15.00-±-1.20
5	31.70 ± 1.27	14.30 ± 1.20	1.17 ± 0.05	130 ± 1.50	15.00-±-0.80
6	34.30 ± 1.32	15.10 ± 0.99	1.18 ± 0.05	111 ± 2.40	15.00-±-1.10
7	28.90 ± 1.20	11.80 ± 0.75	1.13 ± 0.01	130 ± 1.80	1.08-±-0.04
8	32.00 ± 1.20	13.70 ± 0.86	1.16 ± 0.02	125 ± 2.60	2.10-±-0.46
9	33.70 ± 1.24	17.50 ± 0.75	1.21 ± 0.04	138 ± 0.80	2.08-±-0.66
10	34.80 ± 1.26	18.50 ± 0.96	1.23 ± 0.01	128 ± 1.20	15.00-±-1.40
11	29.70 ± 1.18	15.70 ± 0.55	1.19 ± 0.01	130 ± 2.00	2.00-±-0.04
12	32.90 ± 1.27	20.40 ± 0.87	1.26 ± 0.03	127 ± 2.50	15.00-±-1.20
13	31.50 ± 1.16	17.50 ± 0.56	1.21 ± 0.05	132 ± 1.80	3.03-±-0.46
14	31.50 ± 1.19	17.50 ± 0.60	1.21 ± 0.04	130 ± 1.60	8.15-±-0.26
15	31.70 ± 1.22	19.60 ± 0.68	1.24 ± 0.05	129 ± 0.80	4.00-±-0.48
16	28.00 ± 1.30	17.50 ± 0.59	1.21 ± 0.03	130 ± 1.90	8.07-±-0.28
17	31.80 ± 1.32	15.70 ± 0.79	1.19 ± 0.01	130 ± 2.20	1.02-±-0.06
18	29.90 ± 1.35	21.40 ± 0.56	1.27 ± 0.01	130 ± 2.40	3.03-±-0.64

AR – Angle of repose, CI – Carr's index, HR – Hausner's ratio, DT – Disintegration time, CS – Crushing strength

Model Selection and Analysis

Summary statistics for model selection for each response variable is provided in Table V. Model selection for each response was made using the Design Expert ver. 12. Multiple regression analysis was used to correlate the response variables with the input variables investigated. The best-fitting model for each response was selected based on the goodness of fit statistic (r^2). The r^2 values obtained for the responses were ranked in the following order, CS > DT > AR > CI > HR with CS having the highest value of 0.73. This implies that the model selected for CS (linear) can explain 73 % of the variation observed in CS across the preliminary formulations. The significance of each model selected for the various responses was validated by ANOVA. The model p-values < 0.05 implies the model is significant. Hence, the model selections for CI and HR were not significant at $p < 0.05$. As a result, these two responses were not considered in searching for an optimal composition of EGE in the design space. The adequate precision statistic measures the signal to noise ratio and values greater than 4 indicates an adequate signal (Alves *et al.,* 2011; Thapa *et al.,* 2017). The responses of AR, DT and CS recorded values of adequate precision more significant than 4, implying that their models can be used to navigate the design space for optimization studies.

The regression models of AR, DT and CS, can be represented by the polynomial equations given below for each response:

$$Y_1(\text{AR}) = 49.05\,X_1 + 29.25\,X_2 + 34.71\,X_3 - 36.60\,X_1X_2 - 53.80\,X_1X_3 + 24.90\,X_2X_3 \quad (9)$$

$$Y_4(\text{DT}) = 1.10\,X_1 + 2.60\,X_2 + 17.37\,X_3 \quad (10)$$

$$Y_5(\text{CS}) = 133.95\,X_1 + 130.97\,X_2 + 121.57\,X_3 + 3.18\,X_1X_4 + 0.5148\,X_2X_4 - 6.96\,X_3X_4 \quad (11)$$

where X_1, X_2, X_3 & X_4 represents the input factor variables of MS, TLC, MST, and MT, respectively.

TABLE V - Model Summary Statistics

Response	Mixture order	Process order	R^2	Adeq. Precision	F-value	p-value	Inference
AR	Q	M	0.624	6.2527	3.99	0.0230	S
CI	SC	M	0.513	4.2467	1.94	0.1620	NS
HR	SC	M	0.510	4.2027	1.91	0.1665	NS
DT	L	M	0.730	12.4392	20.28	<0.0001	S
CS	L	L	0.730	11.0917	6.51	0.0038	S

AR – Angle of repose, CI – Carr's index, HR – Hausner's ratio, DT – Disintegration time, CS – Crushing strength, Q – Quadratic, M – Mean, SC – Special Cubic, L – Linear, S – Significant, NS – Not significant

Effect of EGE composition and mixing time (input variables) on granule and tablet properties (responses)

The effect of EGE composition and MT on granule and tablet properties of paracetamol tablet formulation was quantified using the polynomial equations generated for each response. This equation is useful for identifying the relative impact of the factors by comparing factor coefficients (Chavan, Modi, Bansal, 2015). The equation for Y_1 shows the relative impact of factors X_1, X_2, & X_3 on the angle of repose of paracetamol granules. The linear effect of these factors was significant at $p < 0.05$. However, the interaction effects of X_1X_2, X_1X_3 & X_2X_3 were not significant at $p < 0.05$. The coefficients for all the factors were positive, implying that increasing the concentration of any of the factors while keeping the others constant will increase the angle of repose (AR) of paracetamol granules. However, the size of the coefficient determined the weighted impact of each factor. Factor X_1 (MS) had a higher coefficient (49.05) suggesting that it exerted more influence on the angle of repose of granules compared to the other two factors. Factor X_2 (TLC) exerted the least effect on the angle of repose of granules on the basis of its lower coefficient (29.25) possibly because of its role as a glidant in tablet formulation where it causes a decrease in angle of repose thereby enhancing the flowability of the granules (Pingali *et al.,* 2009).

The impact of factors X_1, X_2, & X_3 on disintegration time (DT) of paracetamol tablets were characterized by a

linear effect significant at $p < 0.05$. Each factor exerted a positive effect on DT based on the coefficients implying that increasing the concentration of any of these factors while keeping others constant will lead to an increase in the disintegration time of tablets. Factor X_3 (MST) had the largest coefficient (17.37) as seen in the equation for DT implying that its impact on DT was by far greater than that of the other two factors. This was expected due to the hydrophobic nature of MST. Therefore, an increase in MST concentration in the formulation will exert a pronounced effect on DT. The effect of MS was the least significant because of its low factor coefficient (1.10). This is consistent with the role of MS as a disintegrant (Odeku, Akinwande, 2012), where an increase in concentration should lead to a decrease in DT. The linear effect of factors X_1, X_2, & X_3 was significant on the response CS at $p < 0.05$. However, the interaction effects of X_1X_4 and X_2X_4 were not significant at $p < 0.05$. The interaction effect of X_3X_4 had a negative effect on CS suggesting that an increase in the concentration of MST with extended mixing time (MT) during lubrication of granules will lower the CS of tablets generated. This was observed in formulations with higher levels of MST and longer MT (5 min) as seen in the preliminary stage. This has been attributed to the ability of MST to coat the granules during lubrication, thereby interfering with interparticulate bonding and bonding strength resulting in tablets with lower CS (Rahmouni *et al.,* 2002). Evaluation of the design shows that there is a strong correlation between the extragranular excipient composition of a formulation in addition to the process variable of mixing time and the granule and tablet properties of any given formulation.

Graphical illustrations of the model relationship for each response are presented as contour and 3D surface plots in Figures 1 – 3. The contour plot for AR (Figure 1A) shows the relationship between the input factor variables and the response. The various sides of the triangular plot represents the axis for each input factor variable and the plot is drawn in such a way that the range of concentration investigated for each variable increases from the axis of the variable to the opposite angle of the contour plot. The contour lines within the plot depicts varying values of AR determined by the interacting combination of the input variables. The plot shows that the blue-coloured regions represents low values of AR while the red-coloured regions corresponds to higher values with intermediate values of AR falling in the green-coloured region. The segment of the contour plot illustrated as a grey triangle represents an area that is outside the experimental range of the design hence, no contour lines are observed. Lower values of AR can be obtained in the low concentration regions of MS, TLC, & MST. It is obvious from the plot that there are critical levels of each factor that must not be surpassed to obtain a relatively low AR that translates to excellent flowability of granules (Ogunjimi, Alebiowu, 2014). Free-flowing granules are a mandatory requirement for tableting hence, the concentration levels of MS, TLC, and MST must be optimized to produce granules with relative low AR (< 30 °). The 3D surface plot (Figure 1B) shows the interplay of two formulation variables (MS & TLC) and process factor (MT) on AR while the third formulation variable (MST) is kept constant. An increase in the concentration of MS and decrease in the concentration of TLC led to a decrease in AR. The plot shows that changing the mixing time from 2 to 5 min does not significantly affect the outcome of AR.

The contour plot for response DT is displayed as Figure 2A. As described above, the contour plot is a triangular graph where each axis is represented by an input variable of the design. The plot shows that the concentration of each variable increases from the axis across the plot to the opposite angle of the graph. Contour lines in the red-coloured region are denoted by higher values of DT while lower values of DT corresponds to contour lines in the blue-coloured region. The grey segment above the plot represents an area that is outside the experimental range of the design and thus did not generate contour lines. The plot shows that increasing the concentration of MS and TLC lowers DT while increasing the concentration of MST increases DT. The optimization goal is to obtain tablets that disintegrate in less than 15 min thus, combination levels of factors having less of MST will be preferred. The 3D surface plot (Figure 2B) showed similar effect with slight increase in DT with increase in MT. This suggests that lower mixing time should be targeted to produce tablets that disintegrate within 15 min.

The contour plot of CS is presented in Figure 3A. The plot shows that an increase in MS and TLC results

in an increase in CS while an increase in MST results in a decrease in CS. Our goal is to maximise the CS of the tablet formulation hence factor combinations containing a lower concentration of MST will be preferred. The 3D surface plot as presented in Figure 3B shows that the process variable (MT) seems to exert a significant effect on CS as longer mixing time leads to lower CS while shorter mixing time leads to higher CS. This indicates that shorter mixing time will be preferred to maximise the CS of tablet formulation.

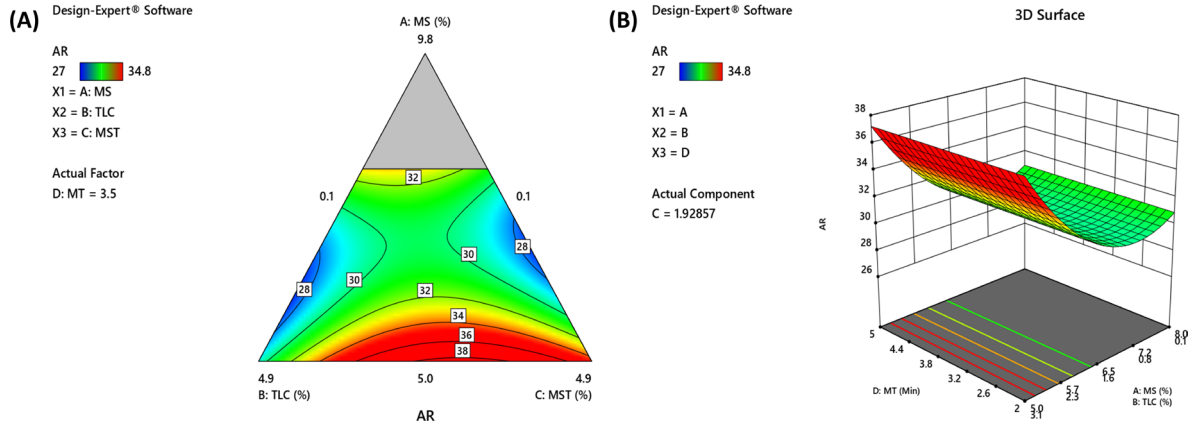

FIGURE 1 - (A) CONTOUR PLOT AND (B) 3D SURFACE PLOT FOR RESPONSE AR.

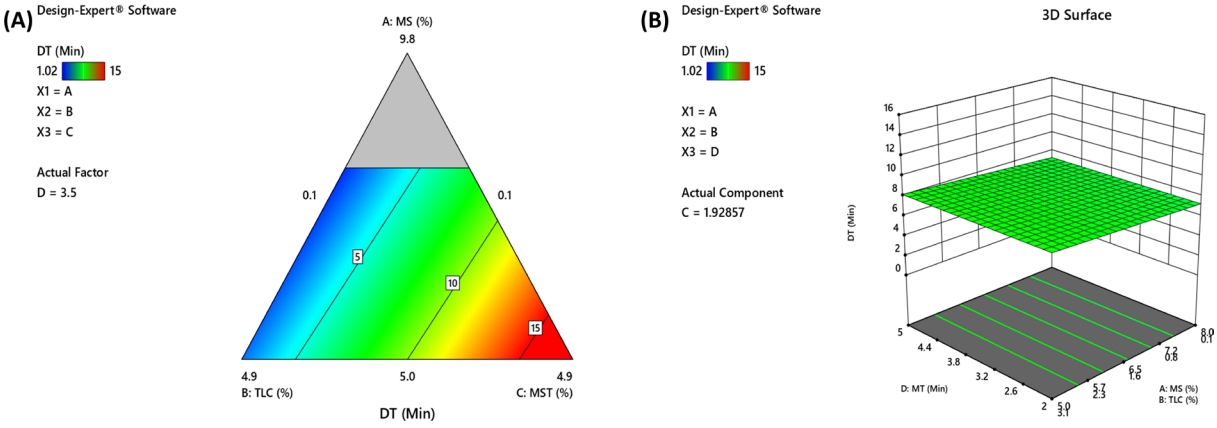

FIGURE 2 - (A) Contour plot and (B) 3D Surface Plot for response DT.

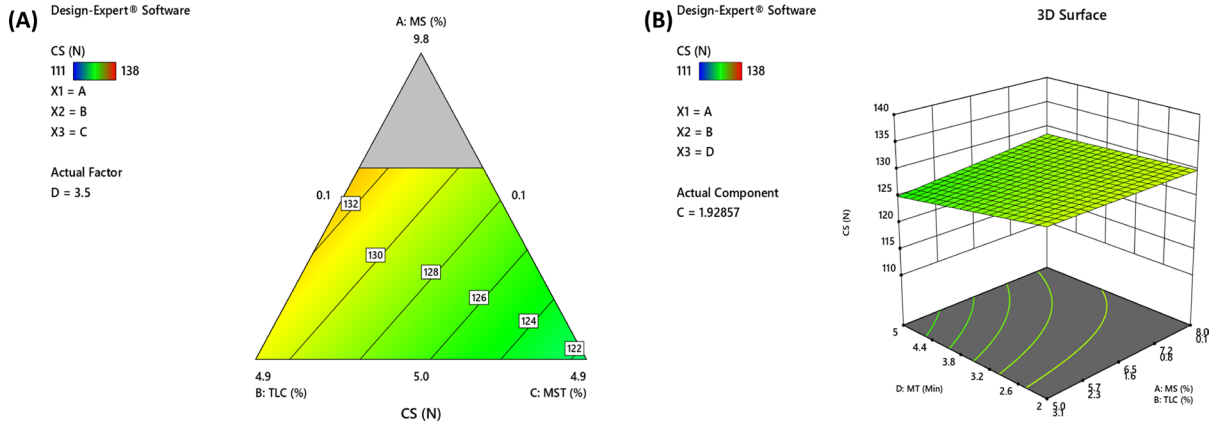

FIGURE 3 - (A) Contour plot and (B) 3D Surface Plot for response CS.

Formulation Optimization

The desired target level for each formulation variable (MS, TLC & MST) and process variable (MT) with the associated responses, AR, DT & CS are summarised in Table VI. The desirability of the model generated was 0.918, indicating that the optimum conditions were located within the limits of the desirability zone.

The responses obtained from the formulation of paracetamol tablet developed using the optimized composition of formulation and process variables given in Table VI are summarised in Table VII. The results shows that the observed values were within the limits of the predicted values thereby validating the design model used to optimize the formulation and process variables of the paracetamol tablet formulation.

TABLE VI - Formulation/Process variables and associated responses

Formulation/ Process Variables				Formulation Responses			Desirability
MS (%)	TLC (%)	MST (%)	MT (min)	AR (°)	DT (min)	CS (N)	
5	4.9	0.1	2	29.25	2.60	130.45	0.918

TABLE VII - Summary of results for Paracetamol tablets using optimum formulation and process variables

Response	Predicted Value	Observed Value	% Predicted Error
AR (°)	29.3	30.2	3.07
DT (min)	2.61	3.01	15.33
CS (N)	130.45	135	3.49

Granule and tablet parameters of Paracetamol tablet formulation

The granule parameters of the optimized and reference formulations of paracetamol tablets is given in Table VIII. Both formulations had similar mean granule size below 500 µm. This falls within the acceptable limits of granule size (250 – 1000 µm) for tableting (Rajani *et al.,* 2017). The flow properties of the granules were characterised by their angle of repose value which was lower for formulation I granules (28.8 °) compared to that of formulation II granules (33.7 °). This can be attributed to the effect of concentration of TLC in both formulations. Talc (TLC) acts as a glidant which lowers interparticulate friction between granules and minimises cohesive interactions thereby lowering the angle of repose. An increase in concentration of TLC from 2 % to 4.9 % produced a greater effect in lowering the angle of repose. The flowability parameters of CI and HR were consistent with the angle of repose as lower values of CI and HR were also obtained for formulation I granules. This implies that there was remarkable improvement in the flow properties of granules prepared by optimization using the DoE approach compared to granules obtained using the OVAT approach.

TABLE VIII - Granule parameters for the optimised and reference formulations

	Formulations	
Parameters	**I**	**II**
Mean granule size (µm)	462.98	478.71
Angle of repose (°)	28.8 ± 0.40	33.7 ± 0.20
Bulk density (g/ml)	0.56 ± 0.02	0.57 ± 0.03
Tapped density (g/ml)	0.63 ± 0.04	0.69 ± 0.01
Carr's Index (%)	11.11 ± 1.20	17.39 ± 0.80
Hausner's ratio	1.13 ± 0.10	1.20 ± 0.20

The tablet parameters for the optimized and reference formulations of paracetamol tablets are summarised in Table IX. Both formulations passed the test for weight variation specified by USP (2008) as the maximum official weight variation for tablets greater than 250 mg is 5 %. Formulation I had a lower mean tablet weight (646 mg) which was closer to the target tablet weight (650 mg).

This implies a lower degree of variation in tablet weight owing to the uniform filling of granules into the die cavity during the tableting process. This was made possible by adopting the DoE approach for optimization. A linear relationship between tablet thickness and tablet weight was established. Tablet thickness has been reported to be influenced by the compression pressure during tableting (Diarra *et al.,* 2013). Formulations having higher tablet weights were also found to have higher tablet thickness (formulation I). Tablet thickness did not differ significantly between formulations possibly because the degree of compressibility of both formulations may have been the same as they were subjected to the same granulation process. The differences in average tablet thickness can be attributed to the slight differences in tablet weight. The crushing strength fell within the same range for both formulations implying that they had the same degree of compressibility. Tablets are said to have passed the friability test if the % difference in tablet weight does not exceed 1 % (USP, 2008). Only formulation I tablets had friability value less than 1 % (0.89 %) which may be attributed to the low concentration of MST in formulation I tablets (0.1 %). Studies have shown that MST exerts a negative effect on the mechanical strength of tablet and therefore contributes to tablet brittleness which renders the tablet more friable (Paul, Sun, 2017). The disintegration time of tablets of formulation I was faster (2.76 min) than those of formulation II tablets (4.72 min). However, both formulations disintegrated within the 15 min limit specified by the official monograph for immediate release conventional tablets (BP, 2013). Shorter disintegration time of tablets from formulation I can be attributed to the lower concentration of MST in the formulation; it is the hydrophobic nature that prevents the uptake of water into the tablet matrix during disintegration. However, with lower concentration of MST in a formulation, the extent of coating of the granules with a hydrophobic film is reduced significantly thereby allowing more rapid uptake of water resulting in faster disintegration time.

The rapid disintegration time of tablets from formulation I was found to influence the rate of drug release (Figure 4). About 80 % of paracetamol was released in 12 min compared to about 80 % being released from the reference formulation in 20 min. This shows that the optimized formulation (Formulation I) had better drug release profile even though the release from the reference was also within the official specification (USP, 2011).

TABLE IX - Tablet parameters for the optimised and reference formulations

	Formulations	
Parameters	**I**	**II**
Weight variation (mg)	646 ± 17.50	676 ± 16.40
Thickness (mm)	5.29 ± 0.10	5.42 ± 0.22
Crushing strength (N)	120 ± 0.00	118 ± 0.42
Friability (%)	0.89	1.19
Disintegration time (min)	2.76 ± 0.80	4.72 ± 0.70
Drug release (T_{80}) (min)	12	20

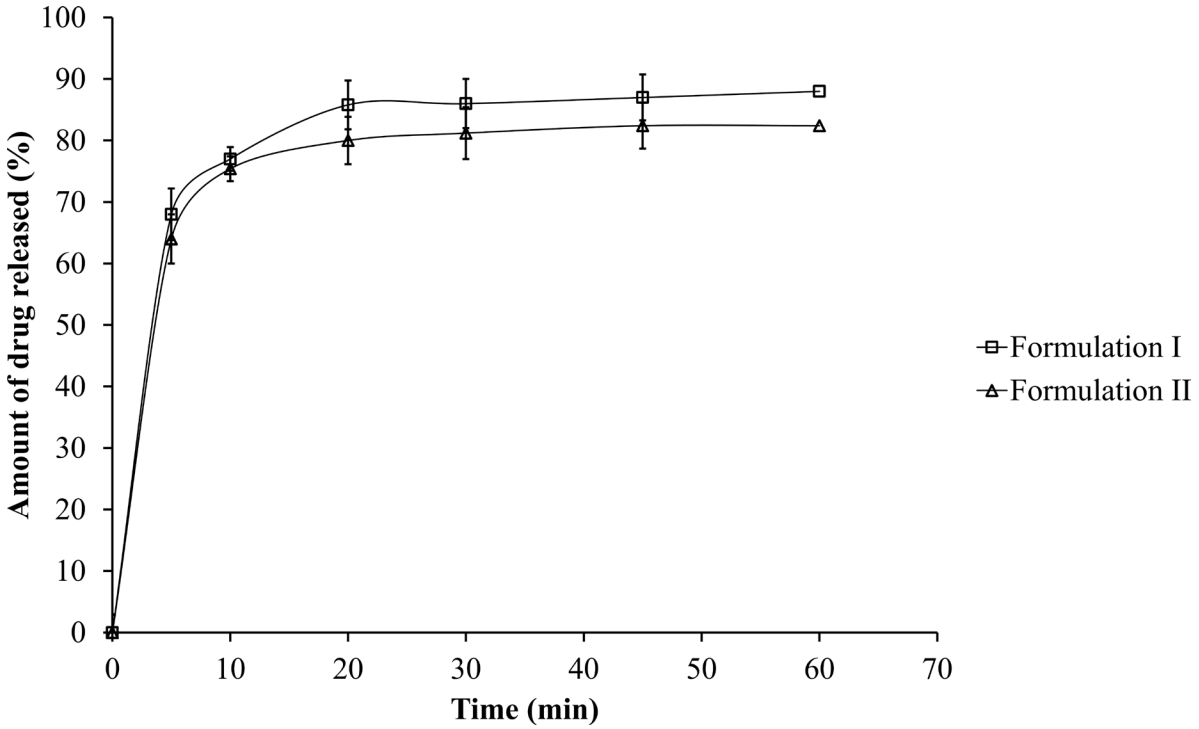

FIGURE 4 - Drug-release profile of formulations I and II.

CONCLUSION

Optimization of the EGE composition and mixing time in paracetamol tablet formulation was carried out using the design of experiment approach. Optimized composition of the extragranular excipient was found to be MS (5 %), TLC (4.9 %) and MST (0.1 %) at a mixing time of 2 min. Granule and tableting properties of the optimized formulation were found to be better than those of a reference formulation whose EGE composition was obtained using the OVAT approach. This study confirmed the relevance of DoE as a tool in pharmaceutical development.

REFERENCES

Alebiowu G, Itiola OA. The influence of pregelatinized starch disintegrants on interacting variables that act on disintegrant properties. Pharm Technol. 2003;27(8):28–33.

Allen L, Popovich N, Ansel H. Powders and Granules. In: Allen L, Popovich N, Ansel H (eds) Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th edn. Lippincott Williams & Wilkins, New York, 2005, pp 186–203.

Almaya A, Aburub A. Effect of particle size on compaction of materials with different deformation mechanisms with and without lubricants. AAPS PharmSciTech. 2008;9(2):414–418.

Alves VML, Sá-Barreto LCL, Souza GHB, Cunha-Filho MSS. Co-processed extracts of Cassia angustifolia Vahl, Fabaceae, and Maytenus ilicifolia (Schrad.) Planch., Celastraceae, for production of high load tablets. Rev Bras Farmacogn. 2011;21(3):510–517.

Andrews GP. Advances in solid dosage form manufacturing technology. Phil Trans R Soc A. 2007;365(1861):2935–2949.

Apeji YE, Olowosulu AK. Quantifying the effect of glidant on the compaction and tableting properties of paracetamol granules. J Res Pharm. 2020;24:44–55.

Bodea A, Leucuta SE. Optimization of hydrophilic matrix tablets using a D-optimal design. Int J Pharm. 1997;153(2):247–255.

British Pharmacopoeia. British Pharmacopoeia, Volume II. Her Majesty's Stationery Office, London, UK, 2013.

Chavan RB, Modi SR, Bansal AK. Role of solid carriers in pharmaceutical performance of solid supersaturable SEDDS of celecoxib. Int J Pharm. 2015;495(1):374–384.

Choudhari PK, Jain HK, Sharma P, Srivastava B. A novel co-processed directly compressible release-retarding polymer:

In vitro, solid state and in vivo evaluation. Futur J Pharm Sci. 2018;4(1):29–40.

Debotton N, Dahan A. Applications of polymers as pharmaceutical excipients in solid oral dosage forms. Med Res Rev. 2017;37(1):52–97.

Desai PM, Liew CV, Heng PWS. Review of disintegrants and the disintegration phenomena. J Pharm Sci. 2016;105(9):2545–2555.

Diarra H, Mazel V, Busignies V, Tchoreloff P. FEM simulation of the die compaction of pharmaceutical products: Influence of visco-elastic phenomena and comparison with experiments. Int J Pharm. 2013;453(2):389–394.

Hartesi B, Sriwidodo, Abdassah M, Chaerunisaa AY. Starch as pharmaceutical excipient. Int J Pharm Sci Rev Res. 2016;41(2):59–64

ICH. Q8(R2) Pharmaceutical Development. 2009

Jadhav N, Paradkar A, Salunkhe N, Karade RS, Mane GG. Talc: a versatile pharmaceutical excipient. World J Pharm Pharm Sci. 2013;2(6):4639–4660.

Kalies A, Heinrich T, Leopold CS. A novel approach to avoid capping and/or lamination by application of external lower punch vibration. Int J Pharm. 2020;580:119195.

Khampeng S, Otsuka M, Peerapattana J. A novel tablet disintegrant from Ocimum canum seeds. J Drug Deliv Sci Technol. 2019;51:18–25.

Miyamoto Y, Ryu A, Sugawara S, Miyajima M, Matsui M, Takayama K, et al. Optimization of the granulation process for designing tablets. Chem Pharm Bull. 1998;46(9):1432–1437.

Odeku OA, Akinwande BL. Effect of the mode of incorporation on the disintegrant properties of acid modified water and white yam starches. Saudi Pharm J. 2012;20(2):171–175.

Ogunjimi AT, Alebiowu G. Neem gum as a binder in a formulated paracetamol tablet with reference to acacia. AAPS PharmSciTech. 2014;15(2):500–510.

Ohwoavworhua FO, Adelakun TA. Non-wood fibre production of microcrystalline cellulose from sorghum caudatum: characterisation and tableting properties. Indian J Pharm Sci. 2010;72(3):295–301.

Patel S, Kaushal AM, Bansal AK. Compression physics in the formulation development of tablets. Crit Rev Ther Drug Carrier Syst. 2006;23(1):1–65.

Paul S, Sun C. Lubrication with magnesium stearate increases tablet brittleness. Powder Technol. 2017;309:126–132.

Perrault M, Bertrand F, Chaouki J. An experimental investigation of the effect of the amount of lubricant on tablet properties. Drug Dev Ind Pharm. 2011;37(2):234–242.

Pingali K, Saranteas K, Foroughi R, Muzzio F. Practical methods for improving flow properties of active pharmaceutical ingredients. Drug Dev Ind Pharm. 2009;35(12):1460–1469.

Rahmouni M, Lenaerts V, Massuelle D, Doelker E, Leroux JC. Influence of physical parameters and lubricants on the compaction properties of granulated and non-granulated cross-linked high amylose starch. Chem Pharm Bull. 2002;50(9):1155–1162.

Rajani C, Kumar DD, Jaya D, Kumar JA. Effects of granule particle size and lubricant concentration on tablet hardness containing large concentration of polymers. Braz J Pharm Sci. 2017;53(3):1–8.

Rodríguez-amado JR, Lafourcade-prada A, César J, Arranz E, Morris H, Colarte AI, et al. Optimization of a novel tablets' formulation using D-optimal mixture design. African J Pharm Pharmacol. 2015;9(14):474–483.

Roy S, Hasan S, Kumar M. Effect of mode of addition of disintegrants on dissolution of model drug from wet granulation tablets. Int J Pharma Sci Res. 2011;2:84–92. https://www.ijpsr.info/docs/IJPSR11-02-02-12.pdf

Singh B, Kapil R, Nandi M, Ahuja N. Developing oral drug delivery systems using formulation by design: vital precepts, retrospect and prospects. Expert Opin Drug Deliv. 2011;8(10):1341–1360.

Surajit P, Susanta KG. A desirability functions-based approach for simultaneous optimization of quantitative and ordinal response variables in industrial processes. Int J Eng Sci Technol. 2018;10(1):76–87.

Thapa P, Lee AR, Choi DH, Jeong SH. Effects of moisture content and compression pressure of various deforming granules on the physical properties of tablets. Powder Technol. 2017;310:92–102.

United States Pharmacopeia. USP NF. 2008.

United States Pharmacopeial Convention. USP Protocol for Dissolution studies. 2011.

Wang J, Wen H, Desai D. Lubrication in tablet formulations. Eur J Pharm Biopharm. 2010;75(1):1–15.

Yu LX. Pharmaceutical quality by design: Product and process development, understanding, and control. Pharm Res. 2008;25(4):781–791.

Zhang J, Wu CY, Pan X, Wu C. On identification of critical material attributes for compression behaviour of pharmaceutical diluent powders. Materials (Basel). 2017;10(7):845.

Received for publication on 04th July 2020
Accepted for publication on 19th November 2020