Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Suppl 2, 2014

Research Article

POLACRILIN RESIN AS MULTIFUNCTIONAL DIRECT COMPRESSION FILLER FOR PARACETAMOL TABLETS OPTIMIZED BY BOX-BEHNKEN DESIGN

SIRAPRAPA CHANSATIDKOSOL, PRANEET OPANASOPIT, TANASAIT NGAWHIRUNPAT, PRASERT AKKARAMONGKOLPORN*

Pharmaceutical Development of Green Innovations Group (PDGIG), Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand. Email: prasert@su.ac.th

Received: 26 Dec 2013, Revised and Accepted: 17 Feb 2014

ABSTRACT

Objectives: The applicability of polacrilin resin as a multifunctional direct compression filler for paracetamol tablets was investigated.

Methods: Box-Behnken design and response surface method were used to evaluate the effect of formulation variables i.e. amount of resin (X_1; 125-375 mg), fumed silica (X_2; 0-1 %) and compression force (X_3; 3-5 ton) on various tablet properties i.e. thickness, hardness, friability, disintegration time and drug release at 30 min, and also to establish the optimum paracetamol tablet.

Results: Paracetamol tablets using polacrilin resin were successfully prepared and their tablet properties were affected by the formulation variables. Polynomial equations were generated to relate the formulation variables and tablet properties. Using the software package optimization process, the formulation variables to obtain the optimum paracetamol tablet were as follows: X_1 = 283 mg, X_2 = 0.93 % and X_3 = 4.1 ton. The optimized paracetamol tablet provided the desired tablet properties including rapid disintegration (< 1 min) and drug release (> 93 %) in the absence of a disintegrant.

Conclusion: The present study reinforced that polacrilin was applicable as a multifunctional filler for direct compression tablet.

Keyword: Polacrilin resin, Disintegrant, Paracetamol tablet, Optimization, Box-Behnken design

INTRODUCTION

Tablet manufacturing by direct compression has retained its popularity due to lower cost, processing time, energy and stability concern for actives that are sensitive to heat or moisture [1]. By this method, direct compression fillers are an essential part in the tablet formulation. The filler primarily acts as "a dry binder" that enables, in particular, a poorly compactable drug, to form an adequately strong tablet.

Typical direct compression fillers include cellulose (e.g. microcrystalline cellulose), starch (e.g. corn and rice starches), polyol (e.g. sorbitol), lactose, inorganic salt (e.g. dicalcium phosphate dihydrate). They are used natively or after modification to have improved properties or multifunctions. For examples, Kumar and Medina prepared and investigated novel cellulose II powders as a multifunctional direct compression filler with disintegrant property [2,3]. The ibuprofen tablets using the cellulose II powders provided the accepted disintegration and dissolution qualities for a USP pharmaceutical tablet without the addition of a disintegrant [3].

Poly(methacrylic acid-co-divinylbenzene), a weakly cationic exchange resin, is one of insoluble pharmaceutical excipients specified in USP as "polacrilin" [4]. It is primarily used as drug carrier as well as taste masker for the development of controlled release dosage forms. The resin can also be a disintegrant in the tablet formulation due to its swelling property in water [5].

Recently, Akkaramongkolporn et al. have established a newly pharmaceutical application of the resin as a multifunctional direct compression filler [6]. The resin exhibits good compactibility, undergoing plastic deformation under compression, along with disintegrant property. Using propranolol hydrochloride, a small-dose drug, as a model drug, the tablets prepared by the resin have acceptable hardness, low friability, rapid disintegration and dissolution of the drug in the absence of a disintegrant.

In this research, the applicability of the resin as a newly multifunctional direct compression filler was further probed with the tablet formulations containing paracetamol, a quite large-dose and poorly compactable model drug [7]. The Box-Behnken design and response surface method were used to statistically evaluate the effects of formulation variables i.e. amount of resin, fumed silica and compression force on various tablet properties i.e. thickness, hardness, friability, disintegration time and drug release at 30 min, and also to establish the optimum paracetamol tablet. The Box-Behnken design was chosen since it required fewer runs as compared with the Central Composite Design in case of three experimental variables [8].

MATERIALS AND METHODS

Material

Poly(methacrylic acid-co-divinylbenzene) (Amberlite IRP 64®, Sigma Chemical Co., USA), paracetamol (Mallinckrodt Inc., USA), fumed silica (Aerosil® 200, Evonik Industries AG, Germany), magnesium stearate (Mallinckrodt Inc., USA) were purchased and used as received. The rest of the chemicals used were of analytical grade.

Experimental design and optimization

The design of experimental trials, generation of response functions and optimization of formulation variables were carried out by using Design Expert software package (Version 7.0, Stat-Ease Inc., Minneapolis, MN, USA).

A Box-Behnken design with 3 factors, 3 levels and 17 trials was selected for this optimization study. The design comprised a set points lying at the midpoint of each edge of a multidimensional cube (n = 12) and replicated center points (n = 5). The second order polynomial equation generated for this experimental design was given as

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 \quad (1)$$

where Y_i (i = 1 to 5) is the the measured responses (tablet properties) which were thickness (Y_1), hardness (Y_2), friability (Y_3), disintegration time (Y_4) and release at 30 min (Y_5), respectively. The terms of X_1, X_2 and X_3 represent the experimental factors (formulation variables) including the amounts of resin (125, 250 and 375 mg), fumed silica (0, 0.5 and 1 %) and compression pressures (3, 4 and 5 ton), respectively. The levels of each variable were coded as -1, 0 and -1 for statistical analysis. b_0 is the intercept and b_1 to b_{33} are the regression coefficients of corresponding terms in the equation.

Preparation of tablet

Flat-faced round tablets containing 250 mg paracetamol were prepared using the designed amounts of resin, fumed silica and

compression pressures as presented in Table 1. Having weighed, the portions of paracetamol and resin were blended for 15 min, fumed silica and magnesium stearate (0.5 %) were added, and the mixture was blended further for 5 min. Then, an accurately weighed aliquot equivalent to one tablet containing 250 mg of paracetamol was placed into a hydraulic hand press machine (Specac P/N 15011/25011, UK) and compressed using stainless steel flat-circular punches (12.7 mm in diameter). The tablets were stored in sealed containers until evaluation.

Evaluation of tablet

Ten tablets were separately used for the measurement of thickness, hardness and friability. The thickness and hardness were determined using a multifunctional tablet tester (TBH225TD, Erweka, Germany). The friability was examined using a friabilator apparatus (TA220, Erweka, Germany) by which tablets were tumbled at 25 rev/min for 4 min. Disintegration test was conducted by a USP disintegration tester (ZT323, Erweka, Germany) in deionized water at 37±0.5°C. Dissolution test was determined using a USP dissolution apparatus II (DT728, Erweka, Germany) operated at 50 rev/min. The dissolution medium was 900 ml of phosphate buffer pH 5.8 maintained at 37±0.5°C (9). At 30 min, the supernatant sample was withdrawn, filtered and analyzed for dissolved drug by an ultraviolet spectrophotometer (T60, PG Instruments, UK) at 243 nm. Six tablets from each formulation were employed for disintegration and dissolution tests.

RESULTS AND DISCUSSION

Polacrilin is an insoluble weakly cationic exchange resin derived from copolymerization of mathacrylic acid and divinylbenzene. According to our recent publication [6], the resin mainly comprised irregular agglomerates of polygonal particles with average size of 85 μm. The true, bulk and tapped densities of the resin were found to be 1.37, 0.54 and 0.64 g/ml, respectively.

As compared with microcrystalline cellulose (Avicel PH102), the resin exhibited better flowability and compactibility at high compression pressures applied. In aqueous medium, the resin substantially adsorbed water and accordingly can act as a tablet disintegrant.

Propranolol hydrochloride tablets prepared by using the resin as a direct compression filler rapidly disintegrated and provided a complete drug release without the addition of any disintegrants. In this work, the applicability of the resin as a multifunctional direct compression filler was demonstrated with paracetamol tablets optimized by the Box-Behnken design. The designed formulation trials along with independent variables and the observed responses are shown in Table 1. Multiple regression analysis ($p < 0.05$) was preformed on these data to generate polynomial response equations and relevant statistical values, as summarized in Table 2. Coefficients of various terms in each equation indicate the effect of formulation variables on a considered response. A positive value of coefficients represents an favorable effect, while a negative one demonstrates an unfavorable effect on responses. The coefficient of determination (R^2) is an indicator of the fit of generated equations [8,10].

All formulation trials of paracetamol tablets were successfully prepared without capping, exhibiting similar diameters (12.76-12.89 mm). The thickness (Y_1) was found to be in the range of 2.65-4.47 mm and the polynomial equation developed for Y_1 is presented in Table 2. The obtained p-value and R^2 of this regression model were < 0.0001 and 0.999, respectively, indicating that the equation was significant ($p < 0.05$) and valid for Y_1. The three-dimensional response surface plot for Y_1 was also depicted, as presented in Figure 1, to graphically display the effect of formulation variables (X_1-X_3) on this response.

Table 1: Variables and observed responses in Box-Behnken design

Trial	Actual value (Coded value)			Thickness (Y_1, mm)	Hardness (Y_2, kg)	F* (Y_3,%)	DT* (Y_4, sec)	Drug release (Y_5, %)
	X_1 (mg)	X_2 (%)	X_3 (ton)					
1	250 (0)	1 (+1)	3 (-1)	3.54	8.5	1.69	23.94	93.50
2	125 (-1)	1 (+1)	4 (0)	2.72	4.07	1.74	11.59	84.33
3	250 (0)	0 (-1)	3 (-1)	3.63	4.67	3.21	17.20	93.41
4	250 (0)	0 (-1)	5 (+1)	3.53	12.78	2.69	20.94	94.38
5	375 (+1)	0.5 (0)	5 (+1)	4.46	16.31	1.00	33.33	96.32
6	250 (0)	0.5 (0)	4 (0)	3.57	9.81	1.27	24.11	84.63
7	125 (-1)	0.5 (0)	3 (-1)	2.72	3.36	3.62	11.32	82.99
8	250 (0)	1 (+1)	5 (+1)	3.55	12.04	0.95	36.71	95.48
9	125 (-1)	0 (-1)	4 (0)	2.68	3.01	100	12.31	83.75
10	375 (+1)	1 (+1)	4 (0)	4.37	14.9	0.86	26.13	94.38
11	375 (+1)	0 (-1)	4 (0)	4.47	7.41	0.92	26.36	97.70
12	250 (0)	0.5 (0)	4 (0)	3.51	9.38	0.97	22.70	93.54
13	250 (0)	0.5 (0)	4 (0)	3.53	8.69	1.52	21.89	93.93
14	250 (0)	0.5 (0)	4 (0)	3.53	10.67	1.58	21.90	92.85
15	125 (-1)	0.5 (0)	5 (+1)	2.65	5.2	2.25	10.85	94.42
16	375 (+1)	0.5 (0)	3 (-1)	4.55	12.52	1.10	26.63	96.06
17	250 (0)	0.5 (0)	4 (0)	3.54	10.81	1.57	22.54	92.92

** F = friability, DT = disintegration time*

Table 2: Polynomial equations generated for various responses

Coefficients	Thickness (Y_1)	Hardness (Y_2)	F* (Y_3)	DT* (Y_4)	Drug release (Y_5)
b_0	3.536	98.720	1.382	22.628	91.574
b_1	0.885	44.375	-0.844	8.298	4.871
b_2	-0.016	14.550	-0.575	2.695	-0.194
b_3	-0.031	21.600	-0.341	2.843	1.830
b_{12}	-0.035	16.075	0.305	0.123	-0.975
b_{23}	-0.005	4.875	0.318	1.793	-2.793
b_{13}	0.028	-11.425	-0.055	2.258	0.253
b_{11}	0.028	-13.373	0.055	-3.848	-1.640
b_{22}	-0.004	-11.873	0.198	0.317	0.106
b_{33}	0.031	8.128	0.555	1.752	2.513
p-value	< 0.0001	0.0014	0.0023	0.0119	0.1011
R^2	0.999	0.944	0.934	0.890	0.777

F = friability, DT = disintegration time

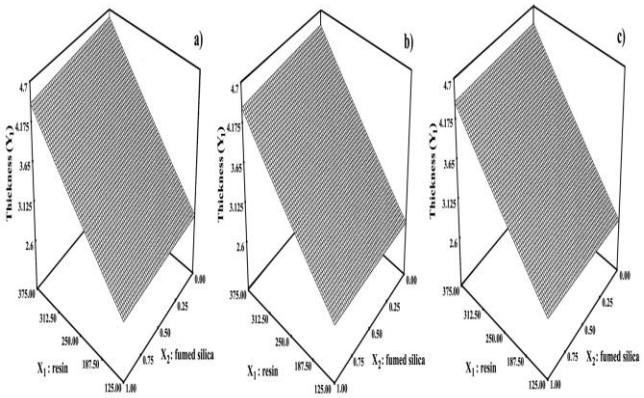

Fig 1: Response surface plots showing the effect of various factors (X_1-X_3) on thickness (Y_1); X_3 = 3 (a), X_3 = 4 and X_3 = 5 ton (c)

According to the equation of Y_1 (Table 2) and Figure 1, the tablet thickness was primarily affected by the amount of resin. The positive value of coefficient (b_1 = 0.885) indicated that the greater amount of resin filler brought about the greater thickness of obtained tablets. Moreover, the thickness was found to directly relate to the tablet weight, as depicted in Figure 2. The amount of fumed silica (b_2 = -0.016) and compression pressure (b_3 = -0.031) provided a slightly negative influence on the thickness. Both of these factors had a promoting effect on the compactibility of ingredients under compression, as described in the next section, thus resulting in the smaller thickness of produced tablets. Coefficients with more than one factor terms (X_1X_2, X_2X_3 and X_1X_3) and those with higher order terms (i.e. X_1^2, X_2^2 and X_3^2) in the generated polynomial equation represent the interaction and quadratic effects of formulation variables on the response, respectively [8,10]. These terms reveal how the thickness changes when two formulation variables are simultaneously changed. The positive coefficients for X_1X_3, X_1^2, and X_3^2 indicated a favorable effect on the thickness, while the negative coefficients for X_1X_2, X_2X_3 and X_2^2 indicated an unfavorable effect on the thickness.

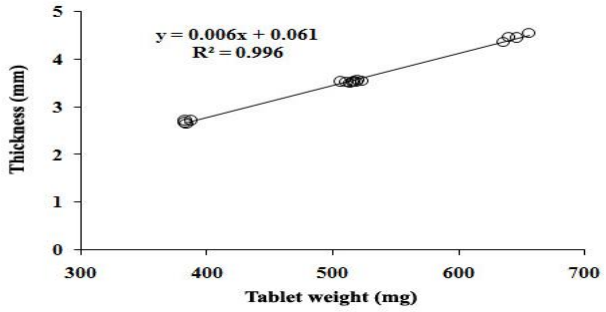

Fig 2: Relationship between thickness and tablet weight of paracetamol tablets

Table 1 presents the hardness (Y_2) for all formulation trials of paracetamol tablets, which was in the range of 3.01-16.31 kg. The polynomial equation and three-dimensional response surface plot developed for Y_2 are shown in Table 2 and Figure 3. The p-value and R^2 were found to be 0.0014 and 0.944, indicating the regression model significant ($p < 0.05$) and fit for Y_2.

From the equation of Y_2 (Table 2) and Figure 3, the hardness was predominantly affected by the amount of resin (X_1), followed by the compression pressure (X_3) and amount of fumed silica (X_2), respectively. An increase in the amount of resin filler resulted in an increase in the hardness of tablets (b_1 = 44.375), confirming the good compactibility of this resin filler. It was reported that the resin was able to form double hydrogen bonds between the carboxyl groups (-COOH) and thus provided a strong interparticle bonding under compression pressure [6]. As expected, the hardness was increased as increasing the compression pressure (X_3; b_3 = 21.600). The higher applied pressure brought particles into the closer contact, as indicated by the decreased thickness, facilitating the formation of interparticle bonding [11]. The incorporation of fumed silica (X_2; b_2 = 14.550) also enhanced the tablet hardness. This agreed with a previous work in which the rice starch physically mixed or co-processed with fumed silica exhibited the increased compactibility (12). The interaction and quadratic terms of X_1X_2, X_2X_3 and X_3^2 positively affected the hardness, while those of X_1X_3, X_1^2 and X_2^2 negatively affected the hardness (Y_2).

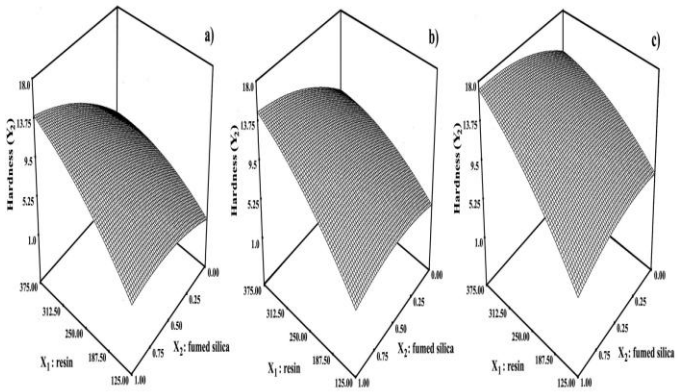

Fig 3: Response surface plots showing the effect of various factors (X_1-X_3) on hardness (Y_2); X_3 = 3 (a), X_3 = 4 and X_3 = 5 ton (c)

The friability (Y_3) was observed in the range of 0.86-3.62 % (Table 1) and the polynomial equation developed for Y_3 is presented in Table 2. The values of p-value and R^2 were 0.0023 and 0.934, respectively, indicating the regression equation significant ($p < 0.05$) and valid for Y_3. The negative coefficients of X_1 (b_1 = -0.844), X_2 (b_2 = -0.575) and X_3 (b_3 = -0.341) indicated an unfavorable effect on the friability. It meant when the amounts of resin, fumed silica and compression force were increased the friability of paracetamol tablets was reduced, as graphically depicted in Figure 4. The reduced friability corresponded to the increased hardness of tablets caused by the resin, fumed silica and compression pressure as described above (Figure 3). The interaction and quadratic terms, except for X_1X_3, indicated a favorable effect on the friability.

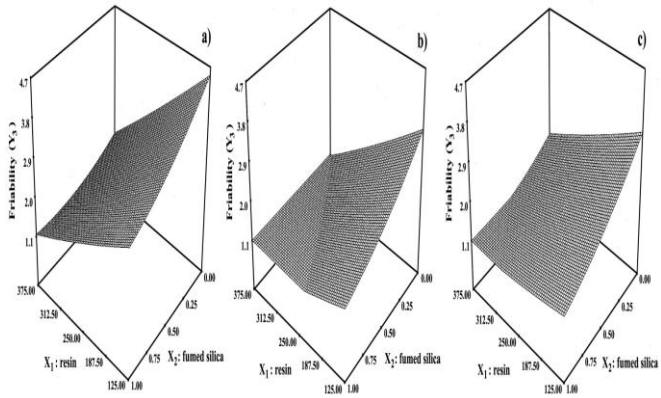

Fig 4: Response surface plots showing the effect of various factors (X_1-X_3) on friability (Y_3); X_3 = 3 (a), X_3 = 4 and X_3 = 5 ton (c)

The disintegration times (Y_4) of paracetamol tablets were found to be in the range of 10.8-36.7 s (Table 1). The polynomial equation and three-dimensional response surface plot for Y_4 are generated and shown in Table 2 and Figure 5. The regression equation was significant and moderately fit for Y_2 as the p-value and R^2 were found to be 0.0119 and 0.890, respectively.

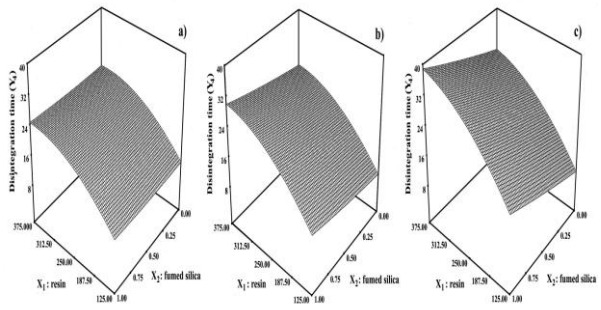

Fig 5: Response surface plots showing the effect of various factors (X_1-X_3) on disintegration time (Y_4); X_3 = 3 (a), X_3 = 4 and X_3 = 5 ton (c)

According to the equation of Y_4 (Table 2) and Figure 5, increasing the amount of resin (b_1 = 8.298), fumed silica (b_2 = 2.695) and compression pressure (b_3 = 2.843) resulted in the increase of disintegration time, which corresponded to the increased hardness of obtained tablets (Figure 3). This is a common tendency that there will be more difficulty for most tablets to disintegrate as their hardness is increased [11]. The interaction and quadratic terms, except for X_1^2, had a positive effect on the disintegration time. Obviously, all formulation trials of paracetamol tablets displayed a very rapid disintegration within 1 min in the absence of disintegrant, which was due to the disintegrant property of the resin filler. This confirmed the resin applicability as a multifunctional direct compression filler. Drug release of paracetamol tablets and polynomial equations (Y_4) were presented in Table 1 and 2, respectively. The regression equations appeared to be insignificant (p-value > 0.05) and poorly fit (R^2 < 0.8) for the release response (Y_5). Probably, the paracetamol tablets disintegrated very rapidly (< 1 min) and thus the drug release sampled at long later time-points (30 min) was independent to the tablet properties determined by the formulation variables (X_1-X_3). With this regard, the release response was considered to be excluded from the construction of response surface plot and the optimization of paracetamol tablet. After studying the effect of formulation variables on the responses, the formulation variables to obtain the optimum paracetamol tablet retaining the following criteria i.e. lowest thickness, highest hardness, lowest friability and shortest disintegration time were carried out by the software package optimization process. The optimized formulation conditions were as follows: X_1 = 283 mg, X_2 = 0.93 % and X_3 = 4.1 ton, and the predicted values of thickness, hardness, friability and disintegration time of the optimum formulation were 3.75 mm, 11.8 kg, 0.86 % and 27.7 sec, respectively. To check this, the optimized paracetamol tablet was prepared and the properties of resultant tablet were determined. The thickness, hardness, friability and disintegration time obtained from the optimized paracetamol tablet were found to be 3.78 mm, 13.9 kg, 0.98 % and 31.5 sec, respectively, which were close to the predicted values. In addition, the optimized paracetamol tablet provided the rapid drug release, which was 96.87, 96.08, 96.97, 93.12, 94.79 and 96.77 % for tested six tablets, complying with the accepted dissolution quality for paracetamol tablet USP monograph (> 85 % at 30 min).

CONCLUSION

Paracetamol tablets using polacrilin as a multifunctional direct compression filler were successfully prepared to provide the desired tablet properties including rapid disintegration and drug release in the absence of disintegrant. Appropriately operational conditions to obtain the optimum formulation of paracetamol tablet could be predicted by the aid of a Box-Behnken design and response surface method. The present study reinforced that polacrilin was applicable as a multifunctional filler for direct compression tablet.

ACKNOWLEGEMENT

The authors wish to thank Silpakorn University Research and Development Institute for funding this research (Grant No. SURDI 55/02/2555), and Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand for instrumental supports.

REFERENCE

1. Bolhuis GK, Chowhan ZT. Materials for direct compression. In: Alderborn G, Nystrom C, editors. Pharmaceutical Powder Compression Technology. New York: Marcel Dekker; 1996. p. 419-500.
2. Kumar V, Reus-Medina ML, Yang D. Preparation, evaluation, and tabletting properties of a new cellulose-based pharmaceutical aid. Int J Pharm 2002;235:129-140.
3. Medina MLR, Kumar V. Evaluation of cellulose II powders as a potential multifunctional excipient in tablet formulations. Int J Pharm 2006;332:31-35.
4. Borodkin S. Ion exchange resins and sustained release. In: Swarbrick J, Boylan JC, editors. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker; 1993. p. 203-216.
5. Bele MH, Derle DV. Effect of sorbed water on disintegrant performance of four brands of polacrilin potassium NF. AAPS PharmSciTech 2012;13:24-34.
6. Akkaramongkolporn, P, Ngawhirunpat T, Opanasopit P. Evaluation of a weakly cationic exchange poly(methacrylic acid-co-divinylbenzene) resin as filler-binder for direct compression tablets. Trop J Pharm Res 2012;13:371-378.
7. Martinello T, Kaneko TM, Velasco MV, Taqueda ME, Consiglieri VO. Optimization of poorly compactable drug tablets manufactured by direct compression using the mixture experimental design. Int J Pharm 2006;322:87-95.
8. Chopra S, Motwani SK, Iqbal Z, Talegaonkar S, Ahmad, FJ, Khar RK. Optimization of polyherbal gels for vaginal drug delivery by Box-Behnken statistical design. Eur J Pharm Biopharm 2007;67:120-131.
9. The United State Pharmacopoeia 29. Rockville MD: United State Pharmacopoeial Convention; 2006.
10. Patel NV, Patel JK, Shah SH. Box-Behnken experimental design in the development of pectin-compritol ATO 888 compression coated colon targeted drug delivery of mesalamine. Acta Pharm 2010;60:39-54.
11. Riippi M, Antikainen O, Niskanen T, Yliruusi J. The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets. Eur J Pharm Biopharm 1998;46:339-345.
12. Kittipongpatana SS, Kittipongpatana N. Preparation and physicochemical properties of co-precipitated rice starch-colloidal silicon dioxide. Powder Technol 2012;217:377-382.