Original Article

Formulation and Optimization of Captopril Sublingual Tablet Using D-Optimal Design

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Abstract

The objective of the current study was to develop and optimize a sublingual tablet formulation of captopril which is an effective drug in the treatment of hypertension. Captopril containing tablets were prepared by direct compression method using different ingredients such as polyvinyl pyrrolidone, starch 1500, sodium starch glycolate and lactose (independent variables) and magnesium stearate, talc and aspartame (fixed components). Tablets were evaluated for the physical properties including hardness, disintegration time and friability which were considered as responses in a D-optimal experimental plan. Results were statistically examined using special cubic model and polynomial mathematical equations and found to be statistically significant (p<0.05) for disintegration time and friability data. Meanwhile linear model was best fitted with hardness data. The obtained results were used to generate optimized overlay plot. The physical data from the numerical optimization were verified and found to be very close to those predicted from the regression analysis. Additional experiments including drug content, in vitro drug dissolution rate and accelerated stability studies were also performed on the optimum formulation. All results were in accordance with the requirements of a sublingual tablet.

Keywords: Captopril; Sublingual tablet; D-optimal mixture design; Optimization.

Introduction

Captopril is a sulfhydryl-containing angiotensin-converting enzyme inhibitor which is used in the management of hypertension, heart failure and myocardial infarction (1). The maximum effect of captopril is produced within 1 to 2 hours after oral doses administration (1, 2) that limits the value of captopril in the treatment of hypertension crisis or acute heart failure (3). Greatly elevated blood pressure occurred in hypertension crisis can result in severe damages

or even death in a short time period, if not treated. In this case, reduction of blood pressure within minutes to 1 hour is necessary (4). Sublingual route is a useful method of administration when rapid onset of action is desired. The ease of usage, patient compliance and improved bioavailability are other advantages of this route (5). It has been reported that sublingual administration of captopril is an effective and safe method of lowering arterial blood pressure in patients with hypertensive emergencies (6-8). Based on previous researches, more rapid attainment of plasma concentration and more rapid onset of pharmacological effect has been observed after sublingual administration of captopril compared

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to oral route (3, 9). Hence, formulation of a sublingual tablet containing captopril could be considered as an appropriate method to obtain suitable clinical effect.

Experimental design, also called design of experiments (DOE), is an approach in the development and optimization of drug delivery devices. By this method, it is feasible to obtain the desired formulation as quickly as possible while avoiding unnecessary experiments (10-12). The major advantage of this method to develop pharmaceutical formulations is that the potential factors could be studied simultaneously, systematically and quickly. By using design of experiments, the effect of each formulation factor on each response can be evaluated and critical factors can be identified based on statistical analysis. When the formulation and manufacturing process of a pharmaceutical product are optimized by a systematic approach using DOE, scale-up and process validation can be very efficient because of the robustness of the formulation and manufacturing process (12). In a mixture experiment, which is suitable for pharmaceutical formulations, the independent factors are the components of a mixture and the response is dependent on the relative proportions of each ingredient (13, 14). It involves changing mixture composition and exploring how such changes will affect the properties of the mixture (15). D-optimal designs can be customized to fulfill classic mixture designs. These designs are more robust to constraints and can produce complex designs with many design constraints.

Unlike standard and classical design of experiments such as factorials and fractional factorials, D-optimal design matrices are usually not orthogonal and effect estimates may be correlated. These types of designs are always an option regardless of the type of model the experimenter wishes to fit. D-optimal designs are straight optimizations based on a chosen optimality criterion and the model that will be fit (13).

Different studies have been conducted on using D-optimal design in optimization of various formulations (16-18), but no published work was found regarding the formulation and optimization of captopril sublingual

tablet. Therefore the present study deals with the optimization of formulation variables using mathematical equations and contour plots to prepare a desired sublingual tablet of captopril with suitable physical and chemical characteristics.

Experimental

Materials
The active ingredient, captopril, was purchased from Arasto Pharmaceutical Chemicals (Iran). The other materials were as follows: starch 1500 (Colorcon, UK), sodium starch glycolate (Agrokemia Sellye, Hungary), polyvinyl pyrrolidone (PVP K10) (Sigma, UK), aspartame (Fluka, Switzerland) lactose, talc, magnesium stearate, phosphoric acid and methanol HPLC grade (Merck, Germany).

Design Expert version 7 (State-Ease Inc., Minneapolis) was used for experimental design and statistical evaluation of the data.

Methods
Planning of a mixture design
In a mixture design, the level of a single component can not be changed independently (19) and the sum of the mixture components has to be equal to 100% (20). Captopril (12.5 mg) tablets were prepared with a constant magnesium stearate (1%), talc (0.2%) and aspartame (1%) and total tablet weight was kept constant (50 mg). Therefore, the experimental range lay between 0 and 72.8% (w/w). The restrictions imposed on the mixture component proportions are shown in Table 1. Experimental ranges were applied in order to comply with the relevant amounts of them actually utilized in commercial pharmaceutical formulations (21). Dependent variables considered in this study were hardness, disintegration time and friability which are shown in Table 2 along with their acceptable ranges for a sublingual tablet.

Tablet preparation
Accurate amount of active ingredient and additives were passed through a no. 35 screen sieve and blended homogeneously. Then magnesium stearate and talc were added to the mixture. The final mixture was converted into

Table 1. Experimental ranges for independent variables and constraints.

Factors	Experimental range		Constraints
	Low value (%)	High value (%)	
X_1 (PVP)	3.69	7.38	$X_1+X_2+X_3+X_4 = 72.5$
X_2 (Starch 1500)	7.38	11.07	$X_1+X_2+X_3+X_4 = 72.5$
X_3 (Sodium starch glycolate)	1.47	5.90	$X_1+X_2+X_3+X_4 = 72.5$
X_4 (Lactose)	48.45	61.26	$X_1+X_2+X_3+X_4 = 72.5$

constant weight tablets by direct compression method using a single punch tableting machine (Erweka AR 4100, Germany) equipped with a 5 mm flat-faced punch and die set.

Tablet drug content

Ten drug containing tablets were powdered, extracted and assayed for drug content individually by HPLC (Merck Hitachi, Germany) (22). Chromatography was performed at room temperature using 4×250 mm L1 column and a mobile phase consisted of methanol:water containing 0.1% phosphoric acid (55:45) with the flow rate of 1 ml/min. The drug was extracted from tablets with the mobile phase and detected in samples by UV detector at 254 nm. The test and standard solutions were protected from exposure to air and were used within 8 hours of preparation.

For content uniformity test 20 tablets were powdered and extracted and the amount of drug in three random samples with the weight equal to 12.5 mg captopril was also determined.

Tablets physical properties evaluation

All formulation tablets were tested for their hardness (Erweka TBH 28, Germany) and friability (Erweka TA 63974, Germany) following the standard methods. The tests were conducted on 10 and 20 tablets respectively. Disintegration test was carried out on six tablets from each formulation using disintegration

Table 2. Dependent variables and the constraints applied on responses.

Responses	Constraints
Y_1 (Hardness)	3.3-4.75 kg
Y_2 (Disintegration time)	20-30 sec
Y_3 (Friability)	0.3-0.8 %

test apparatus (Erweka ZT6-1-D, Germany), at 37±0.5℃ in distilled water as the medium.

In vitro dissolution studies

Dissolution studies were performed for the optimized formulation, employing USP apparatus type II (paddle method, Erweka DT 6R, Germany) at the rotating speed of 50 rpm. Phosphate buffer solution pH 6.8 (500 ml) at 37±0.5 °C was used as dissolution medium (23). Samples (5 ml) were withdrawn at predetermined time intervals and the volume replaced with an equivalent amount of plain medium. The amount of drug dissolved was determined by the HPLC method described above.

Stability studies

Accelerated stability test was conducted on the optimized formulation at 45℃ and 75% relative humidity for 3 months and tablet properties including hardness, disintegration time, friability, drug content and dissolution were determined at the end of each month.

Results and Discussion

Analyzing of mixture data

Table 3 reports the corresponding 20 runs of experimental plan in which the mixture component proportions are indicated. The test mixtures were prepared according to this experimental plan and analyzed for their physical characteristics.

Based on statistical analysis (analysis of variance; ANOVA) (Table 4), a special cubic model (3rd order polynomial model) was chosen for interpreting data results from the D-optimal design for disintegration time and friability. But for hardness response, linear model was fitted to the data ($p < 0.05$).

Table 3. Experimental plan for D-optimal design and results.

Run	Variable factors				Responses		
	X_1	X_2	X_3	X_4	Y_1: Hardness (n=10)	Y_2: Disintegration time (min) (n=6)	Y_3: Friability (%) (n=20)
1	3.69	11.07	1.47	56.37	3.38±1.2	26.00±1.3	1.38
2	4.92	7.38	2.95	37.55	4.00±1.5	17.00±1.5	1.61
3	7.38	5.22	1.90	50.30	4.84±1.9	33.00±1.7	1.38
4	7.38	7.38	1.90	52.14	4.11±0.5	25.00±1.2	1.77
5	5.54	5.22	1.47	56.37	3.99±1.3	21.00±2.5	1.66
6	4.92	7.38	1.90	54.60	3.92±1.8	20.00±1.5	1.38
7	7.38	11.07	1.47	52.00	3.76±1.9	20.00±1.5	1.18
8	5.54	5.22	3.89	54.35	3.60±1.2	35.00±2.3	1.68
9	7.38	7.38	1.47	56.37	5.00±2.5	30.00±1.2	1.78
10	3.69	8.41	4.43	56.08	3.74±1.5	22.00±1.2	1.38
11	5.54	11.07	3.89	52.50	4.33±1.7	25.00±1.5	1.68
12	3.69	11.07	1.47	56.37	3.97±1.2	32.00±1.7	1.38
13	3.69	7.38	1.47	60.26	4.30±1.5	15.00±1.5	1.21
14	3.69	11.07	1.90	52.14	4.30±1.8	30.00±1.9	1.68
15	4.92	7.38	1.90	54.60	4.70±1.5	30.00±1.6	1.52
16	7.38	11.07	1.47	52.00	5.20±1.7	33.60±1.8	1.49
17	7.38	11.07	1.90	48.45	4.73±1.4	40.00±2.2	1.69
18	7.38	7.38	3.89	54.35	3.73±1.1	63.00±1.5	1.58
19	3.69	7.38	1.47	60.26	4.20±1.9	23.00±1.6	1.54
20	3.69	11.07	1.90	52.14	3.83±1.1	30.00±1.7	1.47

The mathematical models generated for the responses Y_1 (hardness), Y_2 (disintegration time) and Y_3 (friability) are as follows:

$$Y_1 = 5.35X_1 + 4.02X_2 + 4.11X_3 + 3.99X_4$$

$$Y_2 = 822.35X_1 - 299.17X_2 - 9.57X_3 + 18.74X_4 - 1162.17X_1X_2 - 2090.37X_1X_3 - 1116.68X_1X_4 + 1146.98X_2X_3 + 511.43X_2X_4 + 71.54X_3X_4 + 2824.40X_1X_2X_3 + 1117.50X_1X_2X_4 + 3016.74X_1X_3X_4 - 1947.89X_2X_3X_4$$

$$Y_3 = -17.99X_1 + 9.73X_2 - 11.65X_3 + 0.39X_4 + 34.52X_1X_2 + 74.88X_1X_3 + 28.18X_1X_4 - 9.91X_2X_4 + 0.25X_2X_3 + 22.70X_3X_4 - 122.47X_1X_2X_3 - 62.80X_1X_2X_4 - 95.15X_1X_3X_4 + 0.17X_2X_3X_4$$

Figures 1a-1c show the response surface plots predicted from the linear model for hardness and special cubic model for disintegration time and friability. In these graphs, the response is shown as the function of PVP, starch 1500 and sodium starch glycolate, having fixed lactose to a value of 55.36% with respect to the total 72.8%. As it was gathered from ANOVA table X_1, X_2, X_3 and X_4 (X_1: PVP, X_2: starch 1500, X_3: sodium starch glycholate and X_4: lactose) were significant model terms in case of hardness. Based on Y_1 equation, it could be concluded that increasing the percentage of all components individually in tablet formulations may result in higher hardness value. However this result was considerable for PVP due to its
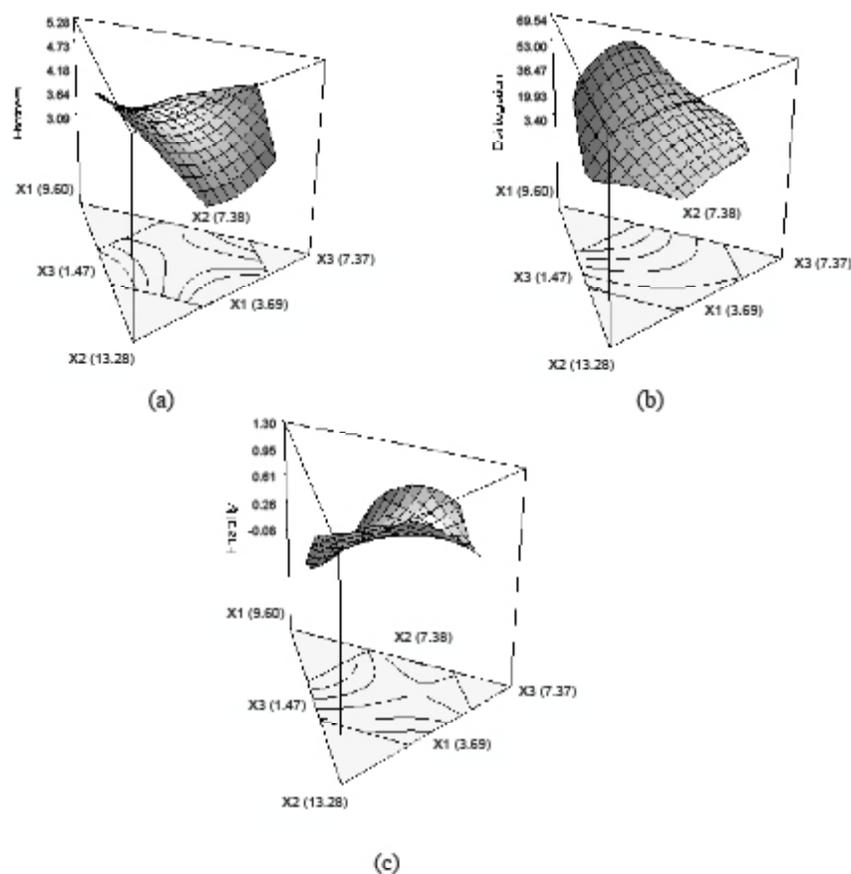
Figure 1. 3D Response surface plots, a: hardness, b: disintegration time and c: friability responses are shown as the function of X_1: PVP, X_2: starch 1500 and X_3: sodium starch glycolate, having fixed the lactose to a value of 55.36%.

binding effect, but the coefficient of the other terms in the mathematical equation shows that the positive effect of other components on hardness value was noticeable. Y_2 equation shows the significant model terms for response of disintegration time. Considering Figure 1b verifies that increasing the amount of PVP in tablet formulations along with decreasing starch 1500 and sodium starch glycolate concentration (with constant ratios) resulted in higher disintegration time. Therefore preparation of fast disintegrating sublingual tablets could be possible by using lower PVP concentrations and higher amount of starch 1500 and sodium starch glycolate in the formulations. Since sodium starch glycolate is a super-disintegrant, the obtained result was expected. Meanwhile, it seems that starch 1500

as a directly compressible starch has a great effect on tablet disintegration time. Significant model terms for response of friability are depicted in equation Y_3. It can be observed from the response surface plot that tablets with lower friability could be prepared by increasing the amount of PVP and decreasing sodium starch glycolate and starch 1500 percentages along with the fixed amount of lactose.

D-optimal optimization results
The aim of the optimization was to obtain the defined targets for all three responses simultaneously with respect to the predefined constraints. At this stage, the defined desirable areas of three responses were superimposed and the region of interest was generated. The overlay plot obtained in optimization procedure is shown

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Table 4. Analysis of variance (ANOVA) of dependent variables.

Source of variation	Sum of squares	Degree of freedom	Mean square	F ratio	P-value
T_1					
Regression	1.66	3	0.22	0.53	0.004
Residuals	3.81	16	0.34		
Lack of fit	2.14	11	0.19	0.58	0.789
adj. R² = 0.89					
T_2					
X_1X_2	458.10	1	458.10	13.40	0.001
X_2X_3	230.86	1	230.86	6.73	0.004
$X_1X_2X_3$	290.76	1	290.76	8.50	0.003
Residuals	25.15	6	3.4		
Lack of fit	12.67	1	12.67	0.33	0.591
adj. R² = 0.87					
T_3					
X_1X_2	0.64	1	0.64	7.24	0.003
X_2X_3	0.61	1	0.61	6.89	0.003
Residuals	0.62	7	0.08		
Lack of fit	0.054	2	0.057	0.29	0.762
adj. R² = 0.51					

* adj. R²: adjusted R-squared.

in Figure 2. The central point of the desired area might be the best point to obtain tablets with suitable properties. Six formulations with high desirability were suggested in this procedure, three of which with desirability more than 93% were prepared and analyzed regarding the responses. Comparative values of predicted and observed responses along with the formulation components were reported in Table 5. Based on the results, the optimized formulations yielded
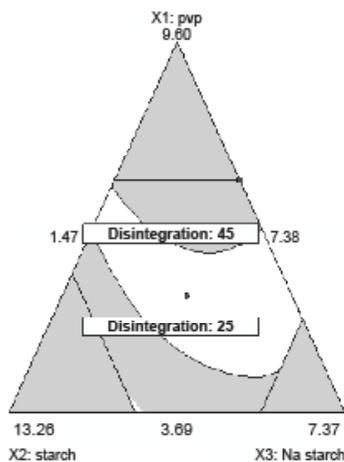

Figure 2. The overlay plot showing the desired area of all three responses containing optimum formulations in white.
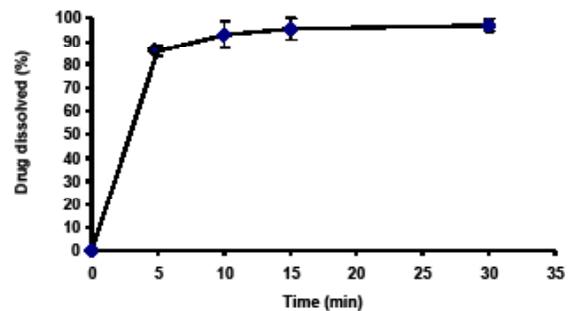

Figure 3. Dissolution profile of captopril from the optimized tablet formulation in phosphate buffer solution pH=6.8 (n=6).

Table 5. Validation step: optimized levels for independent variables and comparative values of predicted and observed responses for optimized numerically formulations.

Formulation	Variable factors				Responses					
	X_1	X_2	X_3	X_4	Y_1 (sc, n=10)		Y_2 (sec, n=6)		Y_3 (%, n=20)	
					Pred.[a]	Obs.[b]	Pred.[a]	Obs.[b]	Pred.[a]	Obs.[b]
O_1	4.22	10.55	1.90	31.73	4.10	4.30±1.7	35	35.00±2.8	0.21	0.23
O_2	5.37	9.57	1.13	32.30	4.20	3.90±2.3	35	35.00±0.7	0.20	0.30
O_3	5.41	9.37	1.15	32.60	4.20	4.30±1.8	35	37.00±2.3	0.20	0.30

[a] Pred.: Predicted values

[b] Obs.: Observed values

responses that were close to the predicted values.

Among the above mentioned formulations, the formulation O_1 was chosen for further studies, due to its desirable physical characteristics as well as good correlation between predicted and observed results for all responses.

Drug Assay

HPLC analysis confirmed the existence of $98 \pm 1.2\%$ of active ingredient in tablets which was in the acceptance criteria provided by US pharmacopeia (22). The results of content uniformity test also showed acceptable and homogenous distribution of drug in tablets.

In vitro dissolution studies

Figure 3 shows the dissolution profile of captopril from the optimized formulation O_1. As shown 5 min after starting the experiment, more than 85% of drug was dissolved in the medium. According to the literature the amount of drug dissolved from sublingual tablets must exceed 80% in 15 min (24). Therefore, the resulted dissolution profile met the above mentioned requirement.

Stability studies

Physical properties of the optimized formulation after keeping in accelerated stability conditions are shown in Table 6. The results revealed that formulation O_1 could be considered stable even after 3 months keeping in accelerated conditions. Figure 4 illustrates the dissolution profiles achieved for tablets after conducting stability experiments which were similar to the freshly prepared tablet and more than 90% of active ingredient was dissolved in the medium 15 min after starting the dissolution study.

Conclusion

An optimized formulation of captopril sublingual tablet was found and prepared in this study by direct compression method. Formulation and optimization procedure was facilitated using D-optimal mixture design. Physico-chemical characteristics and accelerated stability results of the optimum formulation also met all pharmaceutical requirements.

According to the study, although PVP had

Table 6. Physicochemical characteristics of the optimized formulation (O_1) after conducting accelerated stability studies.

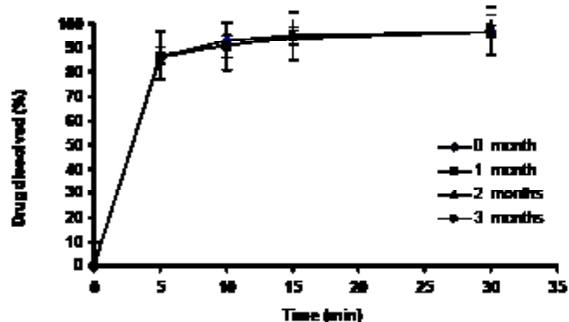| Dependent variable	Time (month)			
	0	1	2	3
Hardness (sc) (n=10)	4.30±1.7	4.38±0.8	4.53±1.7	4.40±0.4
Disintegration time (sec) (n=6)	35.00±2.8	35.00±1.2	37.00±2.5	37.00±4.7
Friability (%) (n=20)	0.23	0.25	0.24	0.24
Drug content (%) (n=3)	98.00±1.2	97.00±1.3	96.00±3.5	95.00±2.7

Figure 4. Dissolution profile of captopril from the optimized tablet formulation after conducting accelerated stability test (n=6).

a signifcant effect on tablet hardness, but increasing all other individual components in the formulations might result in tablets with higher hardness value. On the other hand, formulation of fast disintegrating captopril sublingual tablets could be achieved by using higher amount of sodium starch glycolate as well as starch 1500.

Acknowledgment

References

(1) Sweetman SC. (ed.) *Martinedale, the Complete Drug Reference*. 35th ed., Pharmaceutical Press, London (2007) 1112-1113

(2) Ohman KP, Kagedal B, Larsson R and Karlberg BE. Pharmacokinetics of captopril and its effects on blood pressure during acute and chronic administration and in relation to food intake. *J. Cardiovasc. Pharmacol.* (1985) 7: S20-S24

(3) Al-Furaih TA, McElnay JC, Elborn JS, Rusk R, Scott MG, McMahon J and Nicholls DP. Sublingual captopril-a pharmacokinetic and pharmacodynamic evaluation. *Eur. J. Clin. Pharmacol.* (1991) 40: 393-398

(4) Chetty DJ, Chen LH and Chien YW. Characterization of captopril sublingual permeation: determination of preferred routes and mechanisms. *J. Pharm. Sci.* (2001) 90: 1868-1877

(5) Harris D and Robinson JR. Drug delivery via the mucous membranes of the oral cavity. *J. Pharm. Sci.* (1992) 81: 1-10

(6) Wu SG, Lin SL, Shiao WY, Huang HW, Lin CF and Yang YH. Comparison of sublingual captopril, nifedipine and prazosin in hypertensive emergencies during hemodialysis. *Nephron* (1993) 65: 284-287

(7) Longhini C, Ansani L, Musacci G, Mele D, Vaccari M, Baracca E and Sgobino P. The effect of captopril on peripheral hemodynamics in patients with essential hypertension: comparison between oral and sublingual administration. *Cardiovasc. Drugs Ther.* (1990) 4: 751-754

(8) Angeli P, Chiesa M, Caregaro L, Merkel C, Sacerdoti D, Rondana M and Gatta A. Comparison of sublingual captopril and nifedipine in immediate treatment of hypertensive emergencies; a randomized, single-blind clinical trial. *Arch. Intern. Med.* (1991) 151: 678-682

(9) McElnay JC, Al-Furaih TA, Hughes CM, Scott MG and Nicholls DP. A pharmacokinetic and pharmacodynamic evaluation of buffered sublingual captopril in patients with congestive heart failure. *Eur. J. Clin. Pharmacol.* (1996) 49: 471-476

(10) Mura P, Furlanetto S, Cirri M, Maestrelli F, Marras AM and Pinzauti S. Optimization of glibenclamide tablet composition through the combined use of differential scanning calorimetry and D-optimal mixture experimental design. *J. Pharm. Biomed. Anal.* (2005) 37: 65-71

(11) Hwang RH and Kowalski DL. Design of experiments for formulation development. *Pharm. Technol.* (2005) Dec. 1

(12) Armstrong NA. *Pharmaceutical Experimental Design and Interpretation.* 2nd ed., Taylor & Francis, London (2006) 189-205

(13) Croarkin C, Filliben JJ, Guthrie WF, Heckert A, Tobias P, Prins J, Zey C, Hembree B and Spagon P. *Engineering Statistics Handbook. NIST/SEMATECH e-Handbook of Statistical Methods. Available from:* http://www.itl.nist.gov/div898/handbook/, National Institute of Standard and Technology (2003)

(14) Melas VB. *Functional Approach to Optimal Experimental Design.* Springer, New York (2006) 197-228

(15) Eriksson L, Johansson E and Wikstrom C. Mixture design: design generation, PLS analysis and model usage. *Chemomet. Intell. Lab. Syst.* (1998) 43: 1-24

(16) El-Malah Y, Nazzal S and Khanfar NM. D-optimal mixture design: optimization of ternary matrix blends for controlled zero-order drug release from oral dosage forms. *Drug Dev. Ind. Pharm.* (2006) 32: 1207-1218

(17) Patel SS, Ray S and Thakur RS. Formualtion and evaluation of floating drug delivery system containing clarithromycin for Helicobacter pylori. *Acta Pol. Pharm.* (2006) 63: 53-61

(18) Gonnissen Y, Gonçalves SI, Remon JP and Vervaet C. Mixture design applied to optimize a directly compressible powder produced via cospray drying. *Drug Dev. Ind. Pharm.* (2008) 34: 248-257

(19) Bodea A and Leucuta SE. Optimization of hydrophilic matrix tablets using a D-optimal design. *Int. J. Pharm.* (1997) 153: 247-255

(20) Cornell JA. *Designs Models and the Analysis of Mixture Data.* 2nd ed. J. Wiley and sons, New York (1990) 188-236

(21) Rowe RC, Sheskey PJ and Weller PJ. (eds.) *Handbook of Pharmaceutical Excipients*. 4th ed. Pharmaceutical Press and American Pharmaceutical Association, London (2003) 508, 581

(22) *United States Pharmacopeia, National Formulary* USP29/NF24. The United States Pharmacopeial Convention, Rockville (2006) 367

(23) Ugarkovic SJ. *Sublingual Oral Dosage Form.* US Patent no. 6572891, (2000)

(24) Klancke J. Dissolution testing of orally disintegrating tablets. *Diss. Technol.* (2003) 10(2): 6-8

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