Journal of Applied Pharmaceutical Science Vol. 2 (12), pp. 107-111, December, 2012
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2012.21221
ISSN 2231-3354

Application of Simplex Lattice Design in Formulation and Development of Buoyant Matrices of Dipyridamole

Mandlik Satish K*, Adhikari Saugat, Deshpande Ameya A.
Department of Pharmaceutics, Sinhgad College of Pharmacy, Vadgaon (Bk.), Pune-41, M.S. India.

ARTICLE INFO

Article history:
Received on: 12/11/2012
Revised on: 03/12/2012
Accepted on: 15/12/2012
Available online: 30/12/2012

Key words:
Dipyridamole, Mixture Design, Simplex lattice design, Buoyant matrices, Controlled release, HPMC.

ABSTRACT

The present study describes the design and development of buoyant matrices of dipyridamole. The matrices were prepared by direct compression method using simplex lattice design as an optimization technique. Amount of HPMC K4M (X_1), sodium bicarbonate (X_2) and ethyl cellulose (X_3) were used as the independent variables where floating lag time (Y_1) and percentage drug release at 6h (Y_2) were considered as the response variables. As per the simplex lattice design total 7 formulations were formulated. Matrices were evaluated for physical parameters, *in-vitro* buoyancy, *in-vitro* drug release, water uptake studies. Drug release data was fitted into different kinetic models. The results of response variables were statistically evaluated using design expert 8.0 software. Polynomial models were generated for all the response variables using multiple linear regression analysis (MLRA) approach. A statistical model incorporating 7 interactive terms was used to evaluate the responses. The results of response variables are expressed for model analysis by Scheffe's special cubic model. Graphical representation was done by response surface plots and contour plots. The resulted model equation showed that factor X_1 responsible for prolongation of drug release. On the basis of acceptance criteria the formulation coded by DP3 was selected as a promising formulation from the simplex lattice batches which fitted best to zero order release kinetic model.

INTRODUCTION

There has been considerable research over the last decade on the possibility of controlled and site-specific delivery to the GIT by controlling the gastrointestinal transit of orally administered dosage forms using gastroretentive drug delivery system. Such gastroretentive drug delivery system possesses the ability of retaining the drug in GIT particularly, in the stomach for long periods (Arora *et al.,* 2005). Many drugs show poor bioavailability in the presence of intestinal metabolic enzymes like cytochrome P450 (CYP3A), abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon (Hou *et al.,* 2003). A number of oral controlled release systems have been developed to improve the delivery of drugs to the systemic circulation (Gupta *et. al.,* 2002, Ritchel W.A *et al* 1991).

Although such systems can control precisely and predictably the drug release rate for extended period of time, even over a number of days, they do not always perform satisfactorily if they pass through the drug absorption site e.g. the small intestine, before the release of loaded drug is complete. (Palin *et al* 1985, Hou *et al* 2003) Thus, attention must be given to prolong the residence time of the system to achieve complete drug release in GIT as well as to modulate the drug release rate as predicted by the system in order to obtain an ideal oral control release system (Singh *et al.,* 2000). Several approaches to extend the gastric retention time have been developed including an intragastric floating system, a high density system, bioadhesive polymers (Chitnis *et al.,* 1991), mucoadhesive system (Chowdary *et al.,* 2000), a magnetic system, celluloses, gums (Greminger *et al.,* 1980) and a superporous hydrogel system. An important issue in development of these systems is how to avoid inter-unit and intersubject variations in G.I residence time (Ahuja *et al.,* 1997, Fix *et al.,* 1993). An ion exchange resins loaded with bicarbonate also contributing for gastric retention, which, on contact with media containing hydrochloric acid, release carbon dioxide causing the resin to float (Atyabi *et al.,* 1996).

* *Corresponding Author*
Mandlik Satish K ., Assistant Professor, Department of Pharmaceutics, Sinhgad College of Pharmacy, Vadgaon (Bk.), Pune-41, M.S. India.
Phone: +91-9850187167

Another problem is how to improve the absorption of poorly absorbed drug by using such systems. Various Gastroretentive dosage forms have been formulated against stomach specific *H. pylori* infection (Bardonnet *et al.*, 2006). Variability in G.I transit time is concern for oral controlled drug delivery systems (Gupta *et al* 2002). Drugs with narrow absorption window in GI tract are particularly susceptible to variation in both bioavailability and time to achieve peak plasma levels (Deshpande *et al.*, 1997). Oral controlled release systems continue to be the most popular ones among all the drug delivery systems. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and controlled drug release (Cargill *et. al.*, 1988). Dipyridamole (DP) is a poorly water soluble weak base with pKa of 6.4. DP inhibits thrombus formation when given chronically and causes vasodilation when given at high doses over short time (Pillay *et. al.*, 1998). The extent of absorption of dipyridamole was remarkably lower when gastric pH was continuously elevated to 6.0, whereas absorption increased when gastric pH temporarily decreased to 1.8 (Chen *et al.*, 2000, Timmermans *et al* 1994). So, it would be beneficial to develop floating drug delivery system which prolongs the gastric residence time and releases drug in proximal GI tract where absorption of dipyridamole is more confined and this rationale was considered for preparation of buoyant matrices based on Simple lattice design which is a simplex-shaped design having multiple mixture components. Simple lattice design is a mixture design. (Singh *et.al.* 2004)

MATERIALS AND METHODS

Dipyridamole was received from Zydus Cadilla (Ahmedabad-India), HPMC K4M and Ethyl Cellulose was obtained from Colorcon (Goa-India). Other materials were purchased from the commercial sources: Sodium bicarbonate and lactose from Loba chemie (Mumbai-India), other reagents and solvents used were of analytical grade. Buffer and its dilutions were prepared with double-distilled water.

Experimental design

A Simplex Lattice Design (SLD) was adopted to optimize the formulation variables. In this design 3 factors were evaluated by changing their concentrations simultaneously and keeping total concentration constant (Figure1) (Patel *et. al., 2007,* Prajapati *et al* 2009).

Table. 1: Actual values of coded levels.

Coded levels	Actual values (mg)		
	X_1	X_2	X_3
1	130	80	60
0	70	40	30

The amounts of matrix forming agent (HPMC K4M, X_1), gas-generating agent (sodium bicarbonate, X_2), and floating enhancer (ethyl cellulose, X_3) were selected as independent variables. The preliminary trial batches were carried out to decide the levels of each independent variable (Table 1). The floating lag time (FLT) Y_1 and percentage of drug release at 6th h (%Rel_{6h}) Y_2, were taken as response variables.

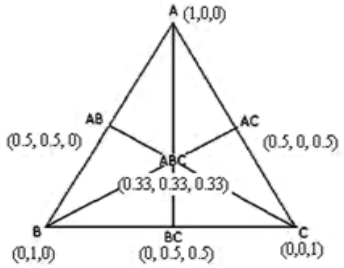

Fig. 1: Simplex Lattice Design.

Preparation of Buoyant Matrices

Different batches of tablets were prepared according to the SLD. Matrix tablets with a constant theoretical weight of 325 mg were obtained using a six station rotary tablet compression machine (JM-6, JMC, Mumbai, India) with flat-faced punches of 11.0 mm diameter. Compaction was accomplished by direct compression of drug-polymers blends previously mixed for 15 min using a tumbler mixer. For each batch, 20 randomly taken tablets were checked for weight uniformity, thickness, hardness and friability.

In vitro dissolution studies

Dissolution studies were conducted in triplicate using standard USP Paddle (Type II) dissolution apparatus (Electrolab). In all the dissolution studies, the paddles were rotated at a speed of 100 rpm in 900 ml simulated gastric fluid (SGF) at 37±0.5 ^{0}C. At appropriate time intervals, 10 ml of the mixture was withdrawn and filtered. The removed samples were analyzed at 284 nm by UV-Vis spectrophotometer (UV 530 JASCO). Dissolution kinetic studies were carried out using PCP DISSO software.

Floating Lag Time (FLT) Study

Tablet immersed in beaker containing 900 ml 0.1 N HCl maintained at 37 ºC. The time required for the tablet to rise to the surface and float was determined as floating lag time (Oth *et. al.* 1992).

Water Uptake (Swelling Index) Study

Swelling systems are studied for the water uptake and subsequent swelling. The swelling behavior of a dosage unit can be measured by studying its weight gain or water uptake (WU). The study is done by immersing the dosage form in simulated gastric fluid at 37 ºC and determining these factors at regular intervals. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time. WU is measured in terms of percent weight gain, as given by the equation,

$$WU = (W_t - W_0) \times 100/W_0$$

in which Wt and W_0 are the weights of the dosage form at time t and initially, respectively. (Li *et al* 2003)

Statistical Analysis and Optimization

The results from simplex lattice design were evaluated using Design Expert 8.0 Software. Polynomial models were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general MLRA model is represented by,

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_{12}X_1X_2 + \beta_{23}X_2X_3 + \beta_{13}X_1X_3 + \beta_{123}X_1X_2X_3$$

Where Y is the dependent variable, β_0 is the arithmetic mean response of the 7 runs, and β_i is the estimated coefficient for the factor Xi. The main effects (X_1, X_2, and X_3) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2, X_2X_3, X_1X_3, and $X_1X_2X_3$) show how the response changes when 2 or more factors are simultaneously changed (Prajapati *et al* 2009). The statistical analysis of the simplex lattice design batches was performed by multiple linear regression analysis using Design Expert V 8.0 software.

RESULTS AND DISCUSSION

Physical Evaluation and Assay of Tablet Formulations

All tablet formulations were evaluated for various physical parameters and assay before proceeding further. The assayed content of drug in various formulations was within limit. (IP Limit- not less than 90% and not more than 110%). Table 2 includes the value of (Mean ± SD) of weights, hardness, thickness and drug content of all 7 formulations prepared using SLD. Thus all physical parameters of the compressed tablets were quite within control.

Table. 2: Physical Evaluation of Different Formulations (DP1-DP7).

Formula-tion	Thickness (mm)	Hardness (kg/cm^2)	Weight Variation (mg)	Drug Content (%)
DP1	2.08±0.04	5.4± 0.21	325±1.2	99.60± 1.19
DP2	2.06±0.06	6.1± 0.36	325±1.3	98.37± 0.95
DP3	2.1±0.03	5.6± 0.69	325±1.1	101.82± 1.13
DP4	2.2±0.01	5.4± 0.29	325±1.4	99.53± 0.86
DP5	2.07±0.04	5.7± 0.71	325±1.2	99.90± 1.12
DP6	2.09±0.03	6.2± 1.21	325±1.3	102.71± 1.10
DP7	2.2±0.08	5.5± 0.42	325±1.2	103.20± 1.23

In-vitro Dissolution Study and FLT Study

The dissolution data of batches DP1 to DP7 were fitted to zero order, first-order, Hixon-Crowell and Korsmeyer and Peppas models. The results of F statistics were used to select the most appropriate model. Cumulative drug release of all formulations is shown in Figure 2.

The mechanism involved in buoyancy of the tablet is the entrapment of carbon dioxide gas induced by sodium bicarbonate after reaction with acidic dissolution medium (0.1N HCl). The gas is trapped and protected within the gel formed by hydration of polymer thus decreasing the density of the tablet below 1gm/cm^3 and the tablet becomes buoyant. The results of response variables are shown in Table 3 the values fo FLT (90.0 to 172 sec) and Rel_{6h} (88.1 to 98.32%), they are strongly depends on independent variables.

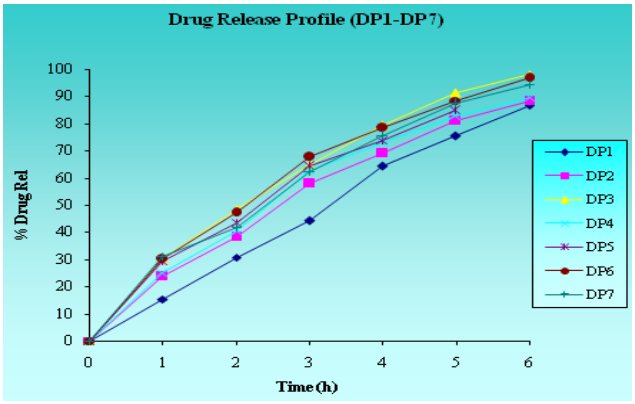

Fig. 2: Drug release profiles of DP1 to DP7.

Table 3: Design Matrix of independent and dependent variables.

Run	Coded Levels of Independent Variables			Response Variables (Dependent Variables)	
	X_1	X_2	X_3	Y_1-FLT (Sec)	Y_2-Rel 6h (%)
DP1	1	1	0	172	86.66
DP2	1	0	1	146	88.1
DP3	0	1	1	107	98.32
DP4	0.5	0.5	0	123	89.68
DP5	0.5	0	0.5	104	92.62
DP6	0	0.5	0.5	90	96.66
DP7	0.33	0.33	0.33	130	94.43

**All batches contained 50 mg DP, lactose to make a tablet 325 mg, 1% magnesium stearate*

Swelling Index (Water Uptake Study)

The swelling behavior of all the formulations was studied. The study was carried out for 6h and the swelling indices at time interval of 1, 2, 4 and 6h were determined. The results of swelling indices are shown in Figure 3.

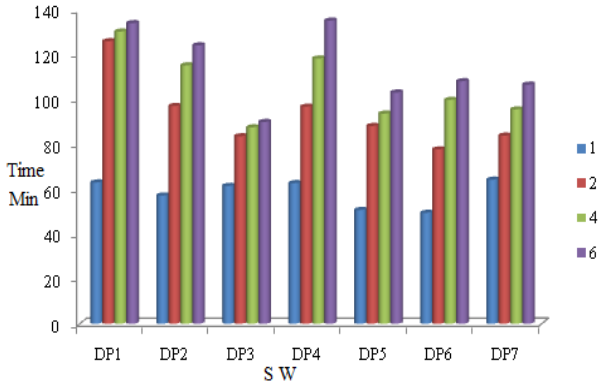

Fig. 3: Water uptake studies of formulations (DP1-DP7) at 1hr, 2hr, 4hr & 6hr respectively.

Mathematical Modeling

The statistical analysis of simplex lattice design batches was performed by MLRA. The results can be expressed for model analysis by Scheffe's special cubic model for two response variables.

FLT- Y_1, (Sec) $= +107.00\ X_1 + 146.00\ X_2 + 172.00\ X_3 - 14.00\ X_1X_2 - 142.00\ X_1X_3 - 276.00\ X_2X_3 + 981.00\ X_1X_2X_3$

REL 6h – Y_2 (%) $= +98.32\ X_1 + 88.10\ X_2 + 86.66\ X_3 - 14.12\ X_1X_2 + 0.52\ X_1X_3 + 37.12\ X_2X_3 + 21.33\ X_1X_2X_3$

Response Surface Analysis

Figures 4A and 5A are the 3D Response Surface Plot, while figures 4B and 5B are the corresponding contour plot for the FLT and Rel_{6h}. The equation for FLT suggests that the factor X_1 has more significant effect on FLT. From the equation of Rel_{6h}, it can be concluded that X_1 has a more important role in prolonging the release. On the basis of acceptance criteria the formulation DP3 was selected as a promising formulation from the simplex lattice batches. These types of plots are useful in study of the effects of two factors on the response at one time.

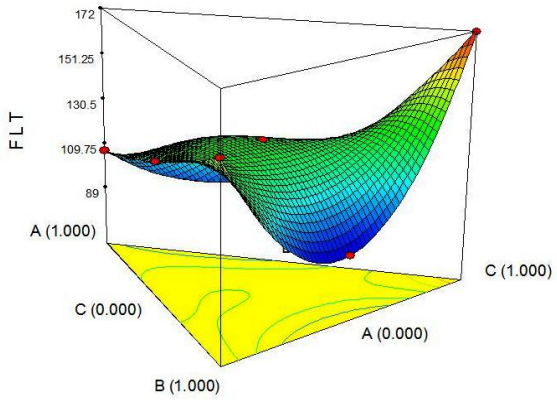

Fig. 4A: Response Surface Plot for Y1- FLT.

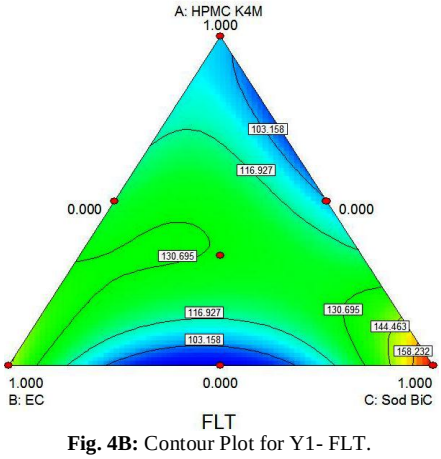

Fig. 4B: Contour Plot for Y1- FLT.

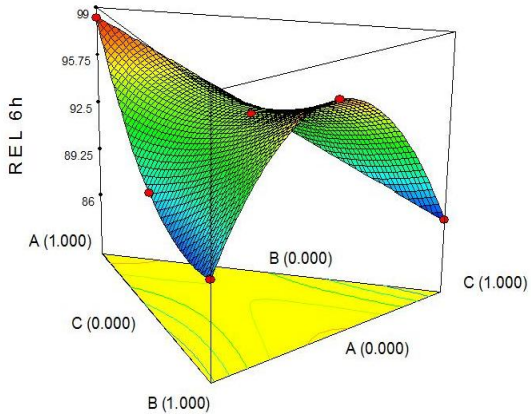

Fig. 5A: Response Surface Plot for Y2- Rel_{6h}.

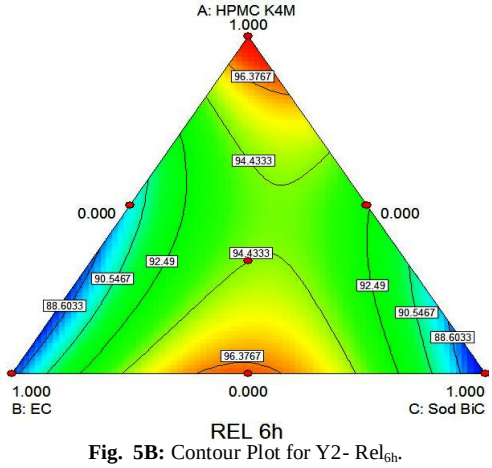

Fig. 5B: Contour Plot for Y2- Rel_{6h}.

CONCLUSION

The floating matrices of Dipyridamole were prepared by direct compression method. Regulated drug release in zero order manner with bounancy of matrices attained in the current study indicates that bouyant matrices of Dipyridamole can successfully employed as floating controlled release drug delivery with minimum experimentation using simplex lattice design. The special cubic model equation for FLT suggests that the factor X_1 has more significant effect on FLT. From the equation for Rel 6h, it can be concluded that X_1 has a more important role in prolonging the drug release retardation. Conclusively, the current study attained that, successful development of dipyridamole, which improves the bioavalability by providing absorption in upper GIT by adopting a systematic formulation approach.

ACKNOWLEGEMENTS

The authors are grateful to Sinhgad Technical Education Society (STES), Pune for providing necessary research facilities. The authors are thankful to Zydus Cadilla (Ahmedabad) and Colorcon (Goa) for providing gift samples of Dipyridamole and HPMC K4M, Ethyl Cellulose respectively.

STATEMENT OF CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

REFERENCES:

Ahuja A, Khar R.K. and Ali J. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm.1997; 23:489-492.

Arora S., Ali J., Ahuja A., Khar R.K. and Baboota S. Floating drug delivery system: A review. AAPS PharmSci Tech. 2005; 6:47

Atyabi F., Sharma H.L., Mohammad H.A.H. and Fell J.T. In Vivo evaluation of a novel gastroretentive formulation based on ion exchange resin. J. Control Rel. 1996; 42: 105-113.

Bardonnet P.L., Faivre V., Pugh W.J., Piffaretti J.C. and Falson F. Gastroretentive dosage forms: overview and special case of helicobacter pylori. J. Control Rel. 2006; 111: 1-18.

Cargill R., Cadwell L.J., Engle K., Fix J.A., Porter P.A. and Gardner C.R. Controlled gastric emptying: I. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs. Pharm. Res. 1988; 5: 533-536.

Chen J., Blevins W.E. and Park K. Gastric retention properties of superporous hydrogel composites. J. Control. Rel. 2000; 64: 39– 51.

Chitnis V.S., Malshe V.S. and Lalla J.K. Bioadhesive polymers-synthesis, evaluation and application in controlled release tablets. Drug Dev. Ind. Pharm. 1991; 17: 879-892.

Chowdary K.P.R. and Srinivas L. Mucoadhesive drug delivery systems: A review of current status. Indian drugs. 2000; 37: 400-403.

Deshpande A.A., Shah N.H., Rhodes C.T. and Malick W. Development of a novel controlled-release system for gastric retention. Pharm. Res. 1997; 14: 815-819.

Fix J.A., Cargill R. and Engle K. Controlled gastric emptying III. Gastric residence time of a nondisintegrating geometric shape on human volunteers. Pharm. Res. 1993; 10: 1087-1089.

Gupta P., Vermani K. and Garg S. Hydrogels: From controlled release to pH-responsive drug delivery. Drug Discovery Today. 2002; 7: 569-579.

Palin K.J. Lipids and oral drug delivery. Pharm. Int. 1985; 11: 272-279.

Ritchel W.A., Menon A. and Sakr A. Biopharmaceutic evaluation of furosemide as a potential candidate for a modified release peroral dosage form. Clin. Pharmacol. 1991; 13: 629-636.

Pillay V. and Fassihi R. Evaluation and comparison of dissolution data derived from different modified release dosage forms: An alternative method. J. Control Rel. 1998; 55: 45-55.

Hou S.Y.E., Cowles V.E. and Berner B. Gastric retention dosage form: A review, Crit. Rev. Ther. Drug Carrier Syst. 2003; 20: 461-497.

Singh B.N. and Kim K.H. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J. Control Rel. 2000; 63: 235-259.

Timmermans J. and Andre J.M. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. J. Pharm. Sci. 1994; 83: 18-24.

Greminger J.K. and Krumer K., Alkyl and Hydroxyalkyl cellulose, In Davidson R.L. Handbook of water soluble gums and resins. 2nd ed. McGraw Hill Book. New York (1980), 3-25.

Oth M., Franz M., Timmermans J. and Moes A. The bilayer floating capsule: a stomach-directed drug delivery system for misoprostol. Pharm. Res. 1992; 9: 298-302.

Li S., Lin S., Daggy B.P., Mirchandani H.L. and Chien Y.W. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int. J. Pharm. 2003; 253: 13-22.

Singh B. and Ahuja N. Response surface optimization of drug delivery system. In Jain NK, editor. Progress in controlled and novel drug delivery system. CBS Publishers and Distributors. New Delhi (2004), 470-509.

Patel D.M. and Patel N.M. Gastroretentive drug delivery system of carbamazepine: Formulation optimization using simplex lattice design: A technical note, AAPS PharmSciTech. 2007; 8(1): 82–86.

Prajapati S. D. and Patel D.L. Floating matrix tablets of domperidone: formulation and optimization using simplex lattice design. Thai J. Pharm. Sci. 2009; 33:113-122.

How to cite this article:

Mandlik Satish K, Adhikari Saugat, Deshpande Ameya A., Application of Simplex Lattice Design in Formulation and Development of Buoyant Matrices of Dipyridamole. J App Pharm Sci. 2012; 2 (12): 107-111.