Medico Research Chronicles

ISSN No. 2394-3971

Original Research Article

DEVELOPMENT OF DELAYED RELEASE PULSATILE DELIVERY SYSTEM FOR NOCTURNAL HYPERTENSION

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Submitted on: January 2018
Accepted on: February 2018
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Abstract:
The aim of the present study was to develop enalapril maleate delayed release polymer-coated pellet formulation as a time-dependent delivery for treatment of hypertension having a close relationship to the chronobiology. Extrusion spheronization technique has been used with box Behnken response surface methodology to study three different factors effect on the robustness of formation i.e. maximum drug release and minimum friability. The concentration of binder showed significant impact on pellet robustness. A further novelty of this work is the use of the combination of pH and time-dependent polymers as a single coating for the development of delayed release pellet formulation. Coating of drug matrix core pellets was optimized by applying a 2-factors 3-levels full factorial design. Continuous dissolution studies were carried out in simulated gastric, intestinal, and colonic fluid with pH 1.2, pH 4.5 and pH 6.8 media respectively. The lag time prior to the drug release was highly affected by a combination of two factors, i.e. the percentage of Eud. RL in coating polymer mixture and coating % level. This experiment demonstrates that the enalapril polymer-coated pellets could be successfully prepared by the design of pH- and time-dependent modified polymer coating to get chronopharmaceutical formulation.

Keywords: Chronobiology; Pulsatile drug delivery; Enalapril maleate; Pellet; Design of experiment

Introduction:

In recent years, chronological control of drug delivery has been of interest to achieve improved drug therapies. Delayed release with a pulse in drug delivery system is having the advantage of avoiding drug tolerance or matching the chrono-therapeutic needs. The oral pulsatile release system was mainly for the treatment of disease symptoms such as hypertension, ischemic heart disease, asthma and rheumatoid arthritis which exhibit circadian rhythms.

The required amount of drug should be released from the drug delivery system at the required time is the aim of the formulation development [1-2].

For a physiological condition showing abnormality/severity in the early morning; a drug delivery system administered at bedtime, but releasing drug during morning hours would be ideal one [3]. Development of pulsatile unit formulations with suitable lag time is of interest in recent days for the betterment of the patient. The recent interest in multiple-unit dosage forms is the result of the advantages they offer over the single-unit systems. Multiple-unit dosage forms offer more predictable gastric emptying, less dependent on the state of nutrition, less variance in transit time through the gastrointestinal tract (GIT), a higher degree of dispersion in the digestive tract, less absorption variability, and a lesser risk of dose dumping than single-unit dosage forms [4-5].

Various pharmaceutical approaches that have been used for targeting the drug to the different part of GIT are mainly based on pH-dependant, time-dependent, and/or bacterially degradable systems. Among these approaches, pH-dependant systems are simple, but the suitability of them for using alone as a colonic delivery in different physiological and pathological conditions in GIT has been doubtful. Therefore, the pH-dependant system was evaluated in combination with the time-dependant system in order to alleviate the pH dependency of former system and to ensure drug release under different physiological conditions [6-7].

The object of the recent study was to develop new pulsatile release formulation of time-controlled or 'site-specific' drug delivery. It suppressed drug release in the stomach and released the drug in the different part of intestine rapidly after a predetermined lag time to give an effective therapeutic drug concentration. The chemistry of combination of two different poly (meth) acrylate as a polymer Eudragit® RL100 (Eud. RL), a time-dependent polymer, and Eudragit® S100 (Ed. S), a pH-dependent polymer, were selected to be the coating material to fit the mentioned purpose.

Material and Method

Material:

Enalapril maleate was a kind gift from Neuland laboratories Ltd (India). Microcrystalline cellulose, Lactose, and Hydroxypropyl methylcellulose (HPMC E 15) were supplied as free gift sample from Signet Chemical Corporation Pvt. Ltd. (India). Eud. RL and Eud. S® was obtained from Rohm Pharma (Gmbh, Germany). Other ingredients such as Triethyl citrate (TEC), dichloromethane (DCM), Isopropyl alcohol (IPA), lubricants and glidants used to prepare the pellets were of the standard Pharmacopoeial grade.

Method:

A) Core pellets

Preparation of Drug-Containing Cores

The cores of the pellets were prepared by an extrusion-spheronization machine. For unit does of the enalapril maleate i.e. 10 mg targeted pellets weight was around 100 mg. MCC, lactose anhydrous and enalapril maleate was mixed sufficiently and was added a certain amount of aqueous solution of HPMC as a binder to make a wet mass which was subsequently extruded through a 0.5 mm screen by the extruder. The extruded material was spheronized with the use of spheronizor at a pre-determined speed to form pellets cores with appropriate diameters. After spheronization, the obtained pellets cores were dried in a fluidized bed for 1 h. The inlet air temperature was 60 °C and the intake flow rate was 0.4 to 0.6 bar. Then the pellets were sieved and the moiety ranging from 24—30

mesh were collected to conduct further polymer coating process.

Optimization of Formulation

In general, formulation variables like the ratio of filler/ diluent (lactose to MCC), the concentration of binder and process variable like the speed of spheroniser are the critical factors which can affect the pellets core property i.e. strength of pellets and drug release from the pellets. The formulation and operating condition of extrusion-spheronization were optimized by Box–Behnken experimental design, to obtain pellets with good strength and provide fast drug release [8-10]. The factors and responses for investigation are shown in Table 1. And Composition as per experimental formulations run is listed in Table2.

Table 1. Factors and Responses Investigated in the Optimization Experimental Design

Factors	**Levels**		
	-1	**0**	**1**
X1 MCC/lactose ratio (w/w)	2	4	6
X2 Binder concentration (% w/w)	2.5	5	7/5
X3 spheronization speed (rpm)	300	450	600
Response	**Constraints**		
Y1 (% drug release in 15 min)	Maximum		
Y2 (% friability)	Minimum		

The degree of friability was evaluated by the weight loss of pellets before and after a rotating drum test. Briefly, about 25 g of pellets were tested for friability in regular friability apparatus at 25 rpm for 10 minutes, after the test, the pellets were sieved and the weight loss from the crash was obtained to estimate the friability as follow:

Equation 1: Friability (%) = (Weight loss / Initial weight) X 100

Drug Release from the Uncoated Cores (in vitro drug release) was studied in a USP dissolution type I. Uncoated drug-containing cores containing 10 mg of enalapril maleate were processed in the baskets. The drug release was investigated in 900 ml pH 6.8 PBS. The rotating rate was 100 rpm and the temperature was 37°C ± 0.5 °C. All the experiments were carried out in triplicates. 10 ml of samples were withdrawn at predetermined time points, filtered by 0.45 PVDF filter discarding first few ml of the filtrate for further processing of determination of content by HPLC. HPLC conditions were as follows: an Inertsil ODS 3V® C18 column (250mm_4.6 mm, 5µm) was used; The mobile phase was a mixture of acetonitrile and phosphate buffer (25/75, v/v); the flow rate was 2.0 ml /min and the column temperature was 50 °C. the detection wavelength is 215 nm [11-12].

Table 2. Composition as per experimental formulations (runs)

Trials	Variable Factors		
	MCC/Lactose ratio	% Binder cocnetration	Spheronisation speed
1	2.00	2.50	450.00
2	6.00	2.50	450.00
3	2.00	7.50	450.00

4	6.00	7.50	450.00
5	2.00	5.00	300.00
6	6.00	5.00	300.00
7	2.00	5.00	600.00
8	6.00	5.00	600.00
9	4.00	2.50	300.00
10	4.00	7.50	300.00
11	4.00	2.50	600.00
12	4.00	7.50	600.00
13	4.00	5.00	450.00

B) Polymer coated pellets

Functional coating of pellets

Optimised formulation of API matrix core pellet was selected and subjected to further processing for functional polymer coating. Six percent (w/w) solutions of polymethacrylates (Eud. RL and Eud. S) were prepared in IPA: DCM (7:3) mixture. Based on the experimental design, experimental formulations run is tabulated in Table 4a, the detailed composition of formulations prepared is given in Table 4b. The solution was plasticized with TEC (≈16%, w/w, with respect to dry polymer), and then talc was added as a glidant. 200 grams of enalapril maleate pellets were coated in a fluidized bed coating apparatus (Pam-Glatt). Coating conditions / parameters are listed in Table 4c. Samples of coated pellets were removed from the apparatus when the coating load had reached 6, 12, and 18% (w/w).

Optimization of coating Formulation

The formulation with respect to the ratio of two different polymer and total percent weight gain was optimized by applying a 2-factors 3-levels full factorial design to obtain pellets with different lag time and provide fast drug release after a lag period. The factors and responses for investigation are shown in Table 3.

Table 3. Factors and Responses Investigated in the Optimization Experimental Design

Factors	**Levels**		
	-1	**0**	**1**
A ratio of Eud. S100 to Eud. RL100	1:0	1:2	1:4
B percentage coating level	6	12	18
Response	**Dependent variable**		
Y3 Lag time	In Hrs		
Y4 (% drug release)	At 6^{th} hr		

Drug release from polymer coated pellets was done by accurately weighed polymer-coated pellets equivalent to 10 mg of enalapril maleate were transferred to the dissolution medium. The test was carried out in a USP dissolution type I assembly, at a rotation speed of 100 rpm in 900 ml medium at 37°C ± 0.5 °C. The media selected for dissolution is pH 1.2 (HCl 0.1 N), followed by pH 4.5 followed by pH 6.8 (phosphate buffer) for 2 h, 2 h, and the remaining 8 h respectively. All the experiments were carried out in triplicates. 10 ml of samples were withdrawn at predetermined time points, filtered by 0.45 PVDF filter discarding first few ml of the filtrate for

further processing of determination of content by HPLC. HPLC conditions were as follows: an Inertsil ODS 3V® C18 column (250mm_4.6 mm, 5µm) was used; The mobile phase was a mixture of acetonitrile and phosphate buffer (25/75, v/v); the flow rate was 2.0 ml /min and the column temperature was 50 °C. the detection wavelength is 215 nm[11-12].

Table 4a. Composition as per experimental formulations (runs)

	Variable Factors	
	Ratio of polymer	% polymer coating
1	-1.00	-1.00
2	0.00	-1.00
3	1.00	-1.00
4	-1.00	0.00
5	0.00	0.00
6	1.00	0.00
7	-1.00	1.00
8	0.00	1.00
9	1.00	1.00
10	0.00	0.00

Table 4b. Composition of experimental runs with detailed formulation

	Polymer ratio (1:4)			*Polymer ratio (1:2)*			*Polymer ratio (1:0)*		
% Coating (w/w)	*6%*	*12%*	*18%*	*6%*	*12%*	*18%*	*6%*	*12%*	*18%*
Unit Composition in mg	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
API loaded Core pellets	70	70	70	70	70	70	70	70	70
Eud. S 100	0.8	1.7	2.5	1.4	2.8	4.2	4.2	8.4	12.6
Eud. RL 100	3.4	6.7	10.1	2.8	5.6	8.4	0.0	0.0	0.0
TEC	0.7	1.4	2.1	0.7	1.4	2.1	0.7	1.4	2.1
Total pellet weight	74.9	79.8	84.7	74.9	79.8	84.7	74.9	79.8	84.7
Total pellet weight with lubrication	76.4	81.4	86.4	76.4	81.4	86.4	76.4	81.4	86.4

Table 4c. Process parameters for pellet coating

Process Parameters	Specifications
Inlet temperature (°C)	45-50
Product temperature (°C)	35-40
Fluidisation (Bar)	0.4-0.6
Coating solution spray rate (g/min)	0.25 - 2
Atomization pressure (Bar)	0.4-0.6
Nossle used (mm)	0.8
Air drying after each % coating stage (min)	10 min

RESULTS AND DISCUSSION

Fundamental structure of the coated pellets

The API loaded core pellets followed by polymer coating were successfully developed using extrusion spheronization and fluidized bed spray-coating systems

respectively. In the extrusion-spheronization process had an efficiency to get > 90 % pellets having minimum fines and agglomerates. In the polymer coating step, the process had an efficiency of ~ 80–85%. The loss of coated product occurred due to the formation of some agglomerates and fines in the product bed, and the loss of coating solids to exhaust. The basic structure of the polymer-coated pellets (final formulation) has been schematically as well as SCM of the same is shown in Figure 1. The release profile of the optimized drug matrixed pellets in pH 1.2, 4.5, and 6.8 is shown in Figure 2. There was more than 90% drug release in 30 min. and friability was minimum. The drug-loaded pellets were further coated with polymeric layer successively using a solvent coating technique. The polymeric layer was the water-insoluble Eud. RL and Eud. S. The purpose of this layer was to act as a barrier to any premature drug release from the delivery system prior to reaching a particular time to provide an appropriate lag phase. It was expected to be a reasonably hydrophobic layer with drug release being controlled by the thickness of the layer.

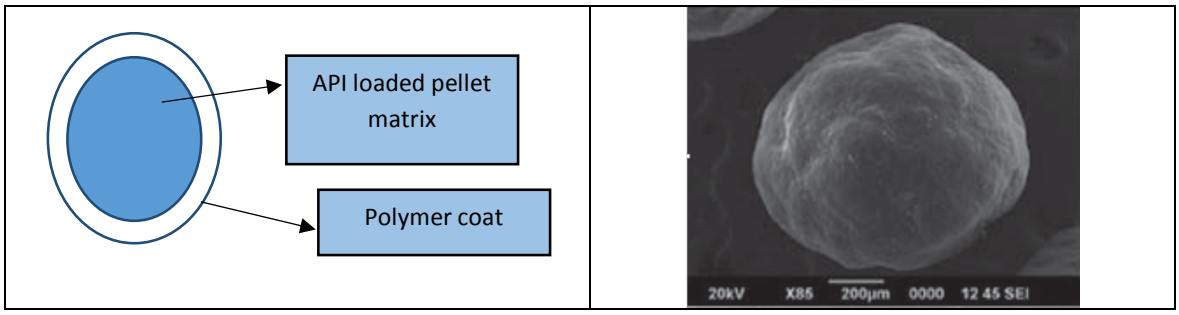

Figure 1: Structure of the final pellets

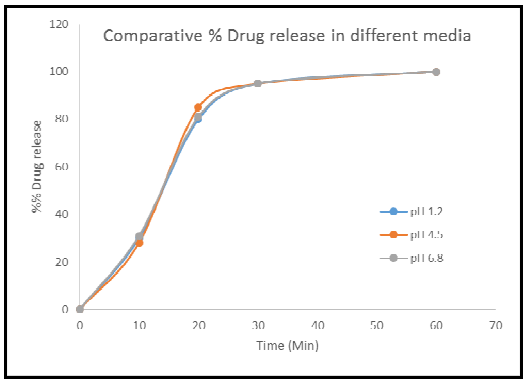

Figure 2: Comparative % Drug release from drug loaded pellets of optimized formulation

Preparation of Drug-loaded Cores and Its Optimization

In the pellet preparation process, both the formulation factor and process factor would affect the properties of the final product, and they might have relationships with each other. Therefore, a 3-factor Box–Behnken experimental design (1 center points, 13 runs) was carried out for optimizing both the formulation and process factors, which were integrated into one experimental group.

The maximum drug release and minimum friability of the pellets were selected as target response of the optimization. Analysis of variance response surface (ANOVA) shown in Table 5 indicated the assumed

regression models were significant and valid for each considered responses. The three-dimensional response surfaces were plotted to estimate the effect of independent variables on each response showed in Figures 3. It can be observed from the plotted figure that the factor binder concentration (X2) is showing significant impact on drug release (Y1) and friability (Y2). Other two factors spheronization time (X3), and MCC/lactose ratio (X1) showed non-significant impact and showing a linear relationship between response Y1 and Y2. Y2 and Y1 were fitted to linear and quadratic model respectively to find the most fitting equation.

Table 5. ANOVA for Response Surface (Actively loaded Core pellets)

Source of variation	Sum of Squares	Degree of freedom	Mean square	F value	P value	Prob > F
Analysis of variance for Y1 (% Drug release)						
Model	1196.08	9	132.90	398.69	0.0002	significant
X1	0.000	1	0.000	0.000	1.0000	
X2	1104.50	1	1104.50	3313.50	< 0.0001	significant
X3	0.50	1	0.50	1.50	0.3081	
X1X2	25.00	1	25.00	75.00	0.0032	significant
X1X3	1.00	1	1.00	3.00	0.1817	
X2X3	4.00	1	4.00	12.00	0.0405	significant
Residual	1.00	3	0.33	--	--	--
Total	1197.08	12	--	--	--	--
Analysis of variance for Y2 (% Friability)						
Model	1.05	3	0.35	44.01	< 0.0001	significant
X1	0.061	1	0.061	7.74	0.0213	significant
X2	0.97	1	0.97	122.03	< 0.0001	significant
X3	0.018	1	0.018	2.28	0.1653	
Residual	0.071	9	7.917E-003	--	--	--
Total	1.12	12	--	--	--	--

The equations of the responses are given below: Final Equation in Terms of Code Factors

Equation 2: Y1 = Drug release = +86.00 +0.000 * X1 -11.75 * X2 -0.25 * X3 +2.50 * X1 * X2 -0.50 * X1 * X3 -1.00 * X2 * X3 +1.50 * $X1^2$ -3.50 * $X2^2$ +1.00 * $X3^2$

Equation 3: Y2 = Friability = +0.65 -0.087 * X1 -0.35 * X2 -0.048 * X3

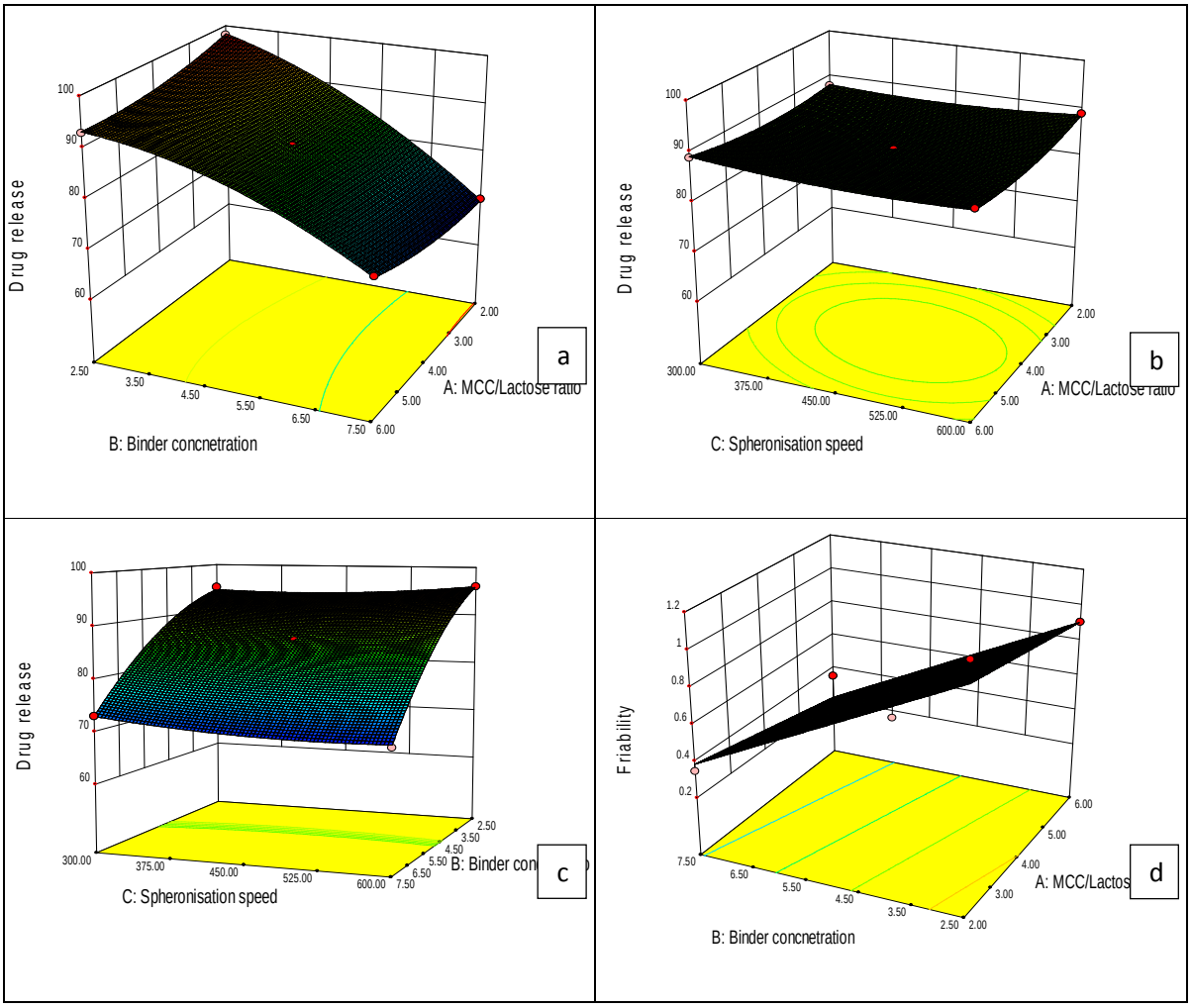

Figure 3: 3D surface response plot: a,b,c is for response drug release and d for response friability against input variables

Polymer coating on Drug loaded Cores and Its Optimization

In the polymer coating of extruded pellets, the formulation variables would affect the properties of the final product. A 3^2 factorial experimental design (1 center points, 10 runs) was carried out for optimizing polymer coating formula, which was integrated into one experimental group. The lag time of drug release and % drug release at 6^{th} hrs from the polymer coated pellets were selected as target response of the optimization

Analysis of variance response surface (ANOVA) shown in Table 6 indicated the assumed regression models were significant and valid for each considered responses. The three-dimensional response surfaces were plotted to estimate the effect of independent variables on each response showed in Figure 4.

Table 6: ANOVA for Response Surface (Polymer coating on drug-loaded pellets)

Source of variation	Sum of Squares	Degree of freedom	Mean square	F value	P value	Prob > F
Analysis of variance for Y3 (Lag time in Hrs)						
Model	64.21	3	21.40	70.69	< 0.0001	significant
A	40.04	1	40.04	132.25	< 0.0001	significant
B	20.17	1	20.17	66.61	0.0002	significant
AB	4.00	1	4.00	13.21	0.0109	significant
Residual	1.82	5	0.36	--	--	--
Total	66.02	9	--	--	--	--
Analysis of variance for Y4 (% drug release at 6^{th} Hrs)						
Model	10683.92	3	3561.31	13.52	0.0045	significant
A	4004.17	1	4004.17	15.20	0.0080	significant
B	4873.50	1	4873.50	18.50	0.0051	significant
AB	1806.25	1	1806.25	6.85	0.0397	significant
Residual	1580.98	6	263.50	--	--	--
Total	12264.90	9	--	--	--	--

The equations of the responses are given below:
Final Equation in Terms of Coded Factors:
Equation 4: Y3 = Lag time = +8.15 -2.58 * A +1.83 * B +1.00 * A * B
Equation 5: Y4 = Drug release (at6 Hr) = +33.10 +25.83 * A -28.50 * B -21.25 * A * B

Figure 4 shows the effect of two formulation factors on lag time and indicates that increase in the ratio of Eud. S rises lag time significantly. Eud. RL is a copolymer of ethyl acrylate, methyl methacrylate, and a low content of a methacrylic acid ester with quaternary ammonium groups (trimethylammonioethyl methacrylate chloride). The ammonium groups are present as salts and make the polymers permeable. Eud. S is a copolymer of methacrylic acid and methyl methacrylate, and the ratio of carboxyl to ester group is ~1:2. Lower ratio of the carboxyl group in Eud. S causes less ionization in neutral to alkaline media than Eud. RL, and hence shows slower solubilization. Also Eur. RL has good swelling properties than Eud. S and Eud. RS [4,6]. The effect of coating thickness on lag time is lesser at low levels of Eud. S and rises at a higher ratio. However, by using proper combinations of Eud. S, Eud. RL, and coating level, the release of drug from formulation after an optimum lag time will be achieved. The drug release profiles of different polymer coated formulations were given in Figure 5.

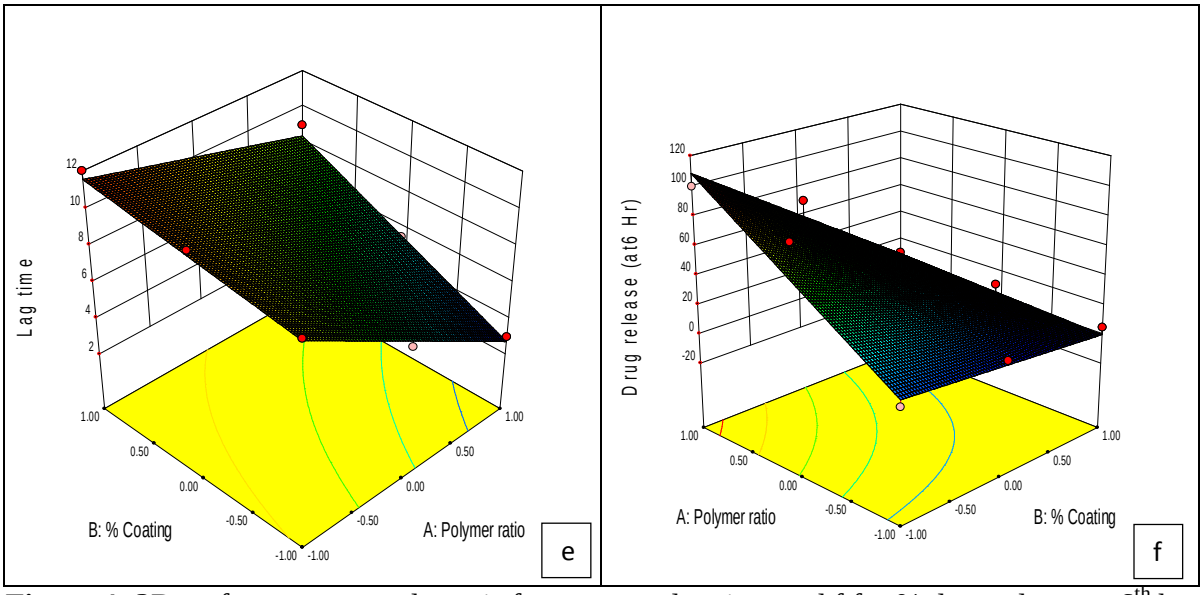

Figure 4: 3D surface response plot: e is for response lag time and f for % drug release at 6th hrs against input variables

A numerical optimization technique using the desirability approach was employed to develop a final formulation with the desired responses. Constraints were applied to the factors (A and B) and (Y3 and Y4) for optimizing the desired formulation. Selected criteria for lag time is 5 hr and % drug release at 6 hrs selected maximum. The optimized formulation (F10) suggested by software was prepared and evaluated for lag time and percentage drug release after 6 h. Drug release profile achieved is shown in Figure 5 with a dotted line graph. Drug release profile of F10 proves the validity of the optimization procedure. The result shows that the observed responses were inside the constraints and close to predicted responses, and, therefore, the factorial design is valid for predicting the optimum formulation. By substituting A and B by the amounts of optimized formulation in equations (4) and (5), predicted responses were obtained.

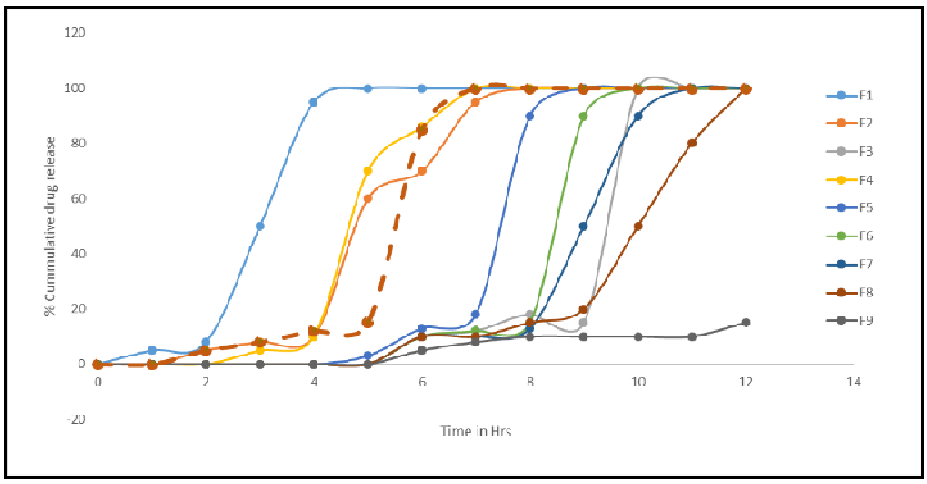

Figure 5: Drug release profile of different polymer coated formulations

Conclusion

The present study concludes that the enalapril maleate polymer-coated pellets could be successfully provide targeted lag time by the design of pH and time-dependent modified chronopharmaceutical formulation. The formulation can be easily optimized by using the factorial design. Pulsatile drug release over a period of 3–12 h, consistent with the requirements for chronopharmaceutical drug delivery, was achieved by mixing different polymer for coating of pellets. Thus, the designed device can be considered as one of the promising formulation technique for preparing a delayed release pulsatile drug delivery system and hence in chronopharmaceutical management of hypertension existing drug molecule can be successfully used by modifying drug delivery system.

References

1) T.Y. Fan*, S.L. Wei, W.W. Yan, D.B. Chen, J. Li., Journal of Controlled Release 77 (2001) 245–251
2) R. Yoshida, K. Sakai, T. Okano, Y. Sakurai, Pulsatile drug delivery system using hydrogels, Adv. Drug Deliv. Rev. 11 (1993) 85–108.
3) Tekade, A.R., Gattani, S.G. Pharm Dev Tech. (2009) 14:380-387.
4) Kadam, V.D., Gattani, S.G. Pharm Dev Tech. (2009). 15:57-63.
5) Kramer, J., Blume, H.. Biopharmaceutical aspects of multiparticulates. In: Ghebre-Sellassie, ed. Multiparticulate oral drug delivery. 1st ed. New York: Marcel Dekker, (1994) 307–32.
6) Chourasia, N.K., Jain, N.K. J Pharm Pharm Sci. (2003) 1:33–66.
7) Schellekens, R.C.A., Stellaard, F., Mitrovic, D., Stuurman, F.E., Kosterinka, J.G.W., Frijlink, H.W. (2008). J Contr Rel. 132:91–8.
8) Yao LIU, Songqing LIU,* and Qing DAI Chem. Pharm. Bull. (2009) 57(1) 55—60
9) Paterakis P. G., Korakianiti E. S., Dallas P. P., Rekkas D. M., Int. J. Pharm., (2002) 248, 51—60
10) Chopra S., Motwani S. K., Iqbal Z., Talegaonkar S., Ahmad F. J., Khar R. K., Eur. J. Pharm. Biopharm., (2007) 67, 120—131.
11) Enelapril maleate tablet monograph; Indian Pharmacopoeia
12) Enelapril maleate tablet monograph; British Pharmacopoeia