FORMULATION AND STASTICAL OPTIMIZATION OF TIME CONTROLLED PULSATILE RELEASE PROPRANOLOL HYDROCHLORIDE COMPRESSED COATED TABLET

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ABSTRACT

The Purpose of present investigation was to evaluate statical influence different concentration of hydroxy propyl methyl cellulose K4M and ethyl cellulose on Propranolol hydrochloride release compression coated tablet using 3^2 full factorial design. Tablets were prepared by direct compression technique. Time controlled pulsatile Propranolol hydrochloride tablets containing 40 mg of Propranolol hydrochloride were developed using different ratio of hydroxypropyl methylcellulose and ethyl cellulose that retard the drug release in the physiological environment of stomach and 2-3 hr in intestine. Formulation was optimized on basis of acceptable tablet properties and in *vitro* drug release. To analyse the release mechanism of optimize batch zero order, first order, Higuchi, Hixson Crowell, Korsmeyer–Peppas kinetic model were used. The kinetics release of optimize batch F3 was best explained by zero order model, Hixson Crowell, and Korsmeyer–Peppas kinetic model.

Keywords:
Propranolol hydrochloride, time controlled pulsatile release, Compression coating, hydroxypropyl methylcellulose, ethylcellulose

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INTRODUCION

Propranolol Hydrochloride is non selective β-adrenergic blocking agent is widely used in the treatment of hypertension, angina pectoris and other cardiovascular disorders[1]. It is almost completely absorbed from following oral administration but its bioavailability has been limited due to extensive first pass metabolism. The short biological half life (3-6 hr) and high frequency of administration initiated to need to

develop once a day control release formulation[1].Therefore, Propranolol Hydrochloride was used as a model drug. Hydrophilic polymer alone for controlling the drug release of highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer[2, 3]. Use of hydrophobic polymers will retard the drug release. So, in the present investigation an attempt has been to formulate time controlled pulsatile release tablets of Propranolol HCl using hydrophilic polymer in combination with hydrophobic polymer. In the present study as a hydrophilic polymer Hydroxypropyl methylcellulose (HPMC) K4M and hydrophobic polymer ethyl cellulose (EC) were used to provide time controlled release of Propranolol Hydrochloride. Ethylcellulose (EC) is a well-known water-insoluble polymer that has long been used as a rate-controlling membrane in medication dosage forms to regulate drug release[4-6]. Whereas HPMC belonging to a water-soluble polymer with the viscous property of gelation might delay the tablet disintegration[2]. The coating was done by compression coating method. The compression-coating technique is one of the novel methods and has been applied for many drugs to develop the site- and/or time-controlled release preparation. This technique has many advantages such as nonsolvent process, short processing time and limited steps, and low labor and energy requirements[7].
The objective of following study was to formulate Propranolol hydrochloride time controlled pulsatile release tablet using HPMC K4M and Ethyl cellulose by compression coating and to elucidate the release kinetics of Propranolol hydrochloride from compressed coated tablets.

MATERIALS AND METHODS

Propranolol Hydrochloride was obtained as gift sample by IPCA laboratory Ltd Selvassa, India. Ethyl cellulose (EC) , Hydroxy propyl methyl cellulose (HPMC),Cross carmellose sodium (Ac-di-sol), Microcrystalline cellulose, Magnesium stearate, Talc was supplied by S. D. Fine Chemicals Ltd., Mumbai, India.

Drug-excipients compatibility studies

Differential Scanning Calorimetry (DSC) of powdered sample of Propranolol HCl and mixture of excipients with drug. DSC analyses of powders were recorded using DSC-Shimadzu 60 with TDA trend line software. The pans were positioned on sample pan holder of a DSC 60. The thermal traces were obtained by heating from 50ºC to 300ºC at heating rate of 10ºC. Thermograms were obtained by the DSC 60 thermal analyzer program and recorded chart speed of 1 inch/min. The thermogram, transion temperature range, the onset of peak transition and the maximum peak of transition were recorded.

3^2 Full Factorial Design

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The Amount of HPMC K4M (X_1) and Amount of Ethyl cellulose (X_2) in Coating layer were selected as independent variables. The times required for 10% (t_{10}) and 90% (t_{90}) drug dissolution were selected as dependent variables. The experimental design with corresponding formulation outline in Table 1.

Table 1: Formulation Design layout for 3^2 full factorial design

Batch code	Variable level in coded form		Variable level in Actual form		Dependent variable	
	X_1	X_2	X_1	X_2	$Y_1(t_{10})$	Y_2 (t_{90})
F1	-1	-1	80	40	1.9	20.2
F2	-1	0	80	60	3.4	21.7
F3	-1	1	80	80	3.06	20.28
F4	0	-1	100	40	4.34	25.25
F5	0	0	100	60	2.95	23.93
F6	0	1	100	80	4.38	26.9
F7	1	-1	120	40	4.74	31.97
F8	1	0	120	60	4.96	34.23
F9	1	1	120	80	5.48	37.31

Where X_1 Amount of HPMC K4M and X_2 Amount of Ethyl Cellulose
Y_1 time require for 10% drug release (t_{10}) and Y_2 time require for 90% drug release (t_{90})
All the batches contain 40 mg of Propranolol HCl

A statical model incorporating interactive and polynomial term was utilized to evaluate response (eqn.1) $Y = b_0 + b_1X_1+b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$ –(1) Where, Y is the dependent variables, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity.

Preparation of Propranolol HCl time controlled pulsatile release tablets
Propranolol HCl core tablets formulations
Tablets of Propranolol HCl were made by direct compression method. All ingredients were weighted accurately and mix well in V-Blender mixer for 15 min. microcrystalline cellulose was used as direct compressing agent. Croscarmellose sodium used as disintegrating/swelling agent. Talc and magnesium stearate were used as lubricant. Tablets were made in minipress tablet machine in concave punch (Diameter 6mm).

Compression Coating of core tablets
Components of the coat were mixed for 10 minutes. Magnesium stearate and talc were added to all batches, with subsequent mixing 10 minutes. Die filling, core centralization and machine operation were undertaken using by a standardized manual process. Half of the powder mass for one tablet coat was weighed into a die. A lower coating layer was consolidated and the core centred on an even bed. The remaining powder was then added to the die and compressed in to tablets using single punch tablet machine (Cadmach machinery, Ahmedabad).

Table 2: Formulation of factorial batches of Propranolol HCl Tablet

Composition of core Tablet									
Ingredient	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Propranolol HCl	40	40	40	40	40	40	40	40	40
MCC	50	50	50	50	50	50	50	50	50
Ac-di-sol	6	6	6	6	6	6	6	6	6
Talc	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2
Composition of compress coating									
HPMC K4M	80	80	80	100	100	100	120	120	120
EC	40	60	80	40	60	80	40	60	80
Talc	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2

Evaluation of Compressed Coated Tablets

Weight variation test:

To study weight variation 20 tablets of each formulation were weighed using a Sartorious electronic balance and the test was performed according to the official method[8].

Hardness and friability

For each formulation, the hardness of 6 tablets was determined using the validated dial type hardness tester and the Roche friabilator (Camp-bell Electronics, Mumbai, India), respectively[8].

Thickness

The thickness of the tablets was determined by using vernier caliperse. Five tablets from each formulation were used and average values were calculated[8].

Uniformity of content:

The Propranolol HCl tablets were tested for their drug content. Comply with the requirements stated under Tablets using the following method of analysis. Transfer one tablet to a 100-ml volumetric flask, add 5 ml of *dilute hydrochloric acid* and allow to stand, swirling occasionally, until it is disintegrated. Add about 70 ml of *methanol* and shake well for about 1 minute. Dilute to volume with *methanol*, mix and centrifuge an aliquot of the solution. Dilute a suitable volume of the clear solution with *methanol* to produce a solution containing 20 m g of Propranolol Hydrochloride per ml. Measure the *absorbance* of the resulting solution at the maximum at about 290 nm[9].

In-vitro drug release studies:

In vitro drug release studies were conducted for all formulation using dissolution test apparatus (Veego UDA-8D USP standard). Drug release studies were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 2, 50 rpm, 37.5 °C) for 2 hr in 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with pH-6.8 phosphate buffer (900 ml) and tested for drug release up to 24 hr. At the end of the each time period 10 ml of the samples

were taken and analyzed for Propranolol HCl content. A 10 ml Volume of fresh and filtered dissolution medium was added to make the Volume after each sample withdrawal. Sample was analyzed using UV spectrophotometer at 290 nm[9, 10].

Drug release kinetic modelling for optimize batch

The rate and mechanism of release of Propranolol hydrochloride from the prepared compressed coated tablets were analysed by fitting the release data into zero-order equation, $C=C_0-K_0t$ (Eq. 1), where Q is the amount of drug released at time t and K_0 is the release rate, First order equation[11], $LogC= LogC_0-Kt/2.303$ (Eq. 2), where K is the release rate constant, Higuchi's equation[12], $Q=Kt^{½}$ (Eq. 3), where Q is the amount of drug released at time t and K is the diffusion rate constant. To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data were also plotted using the Hixson-Crowell cube root law [13], $3\sqrt{Q_0}- 3\sqrt{Q_t} =K_{HC} \times t$ (Eq. 4) where Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in the tablet, and K_{HC} is the rate constant. The release data were also analyzed as per Korsmeyer-Peppas equation[14], $M_t/M_\infty=Kt^n$ (Eq. 5), where M_t/M_∞ is the fractional release of the drug, t is the release time, K is a constant incorporating structural and geometric characteristics of the release device, 'n' is the release exponent indicative of mechanism of release. For non-Fickian (anomalous/ zero order) release, 'n' value is between 0.5 to 1.0, for Fickian diffusion, $n \leq 0.5$; for zero order release, $n = 1$; for super case transport II, $n > 1$; 'n' is estimated from linear regression of log (M_t/M_∞) Vs log t.

RESULTS AND DISCUSSION

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic or exothermic phase transformations). The thermo grams of Propranolol HCl and mixture of excipients with drug showed in Figure 1.

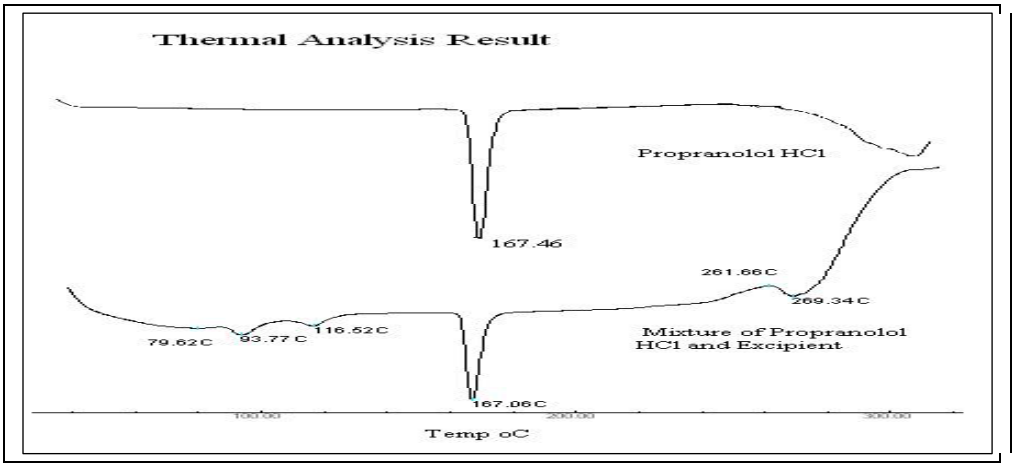

Fig.1: DSC Spectra of Propranolol HCl and Mixture of excipients with drug

The melting point of Propranolol HCl is between 163° and 167° [9]. In DSC Spectra, Propranolol HCl melting peak was shown 167.46 ºC and in physical mixture was present at position i.e. near 167.06 ºC. This confirmed the physicochemical compatibility of drug with the formulation excipients used in the study.

The Present investigation Attempt was made to optimize the suitable ratio of HPMC K4M and EC by applying 3^2 factorial design for compression coating to provide suitable lag time and desire drug release profile in simulated intestinal fluid. Tablets were evaluated for various parameters like Weight variation, Hardness, Friability, Uniformity of content and In vitro drug release.

Characterization of tablets

The hardness and friability of the tablets was found to be in the range of 4-6 kg/cm^2 and 0.5-1.0% respectively**.** Propranolol HCl Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of Propranolol the time release tablets were found to contain 99.5-103.8% of the labeled amount of Propranolol indicating uniformity of drug content.

Table 3: Characterization of tablets

Batch code	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Weight variation (mg)	Drug content (%)
F1	5.2 ± 0.4	0.75± 0.02	2.0 ± 0.05	221 ± 3.56	98.79 ± 0.36
F2	5.6 ± 0.2	0.53± 0.03	2.0 ± 0.05	238 ± 2.94	97.34 ± 0.12
F3	5.3 ± 0.6	0.60± 0.04	2.03 ± 0.02	243 ± 4.31	98.96 ± 0.23
F4	5.2 ± 0.4	0.56± 0.03	2.06 ± 0.03	245 ± 3.84	98.67 ± 0.31
F5	5.3 ± 0.5	0.49± 0.05	2.05 ± 0.02	261 ± 4.26	98.95 ± 0.51
F6	4.9± 0.2	0.5± 0.03	2.04 ± 0.03	283 ± 3.43	99.02± 0.14
F7	5.1± 0.9	0.45± 0.06	2.0 ± 0.05	264 ± 2.29	99.04 ± 0.56
F8	5.0 ± 0.4	0.5± 0.05	2.03 ± 0.02	282 ± 2.72	98.95 ± 0.51
F9	5.1± 0.4	0.5± 0.03	2.07 ± 0.03	301 ± 3.68	96.12± 0.56

In vitro drug release study of Factorial design batches

In vitro dissolution studies are valuable tools to judge quality and stability of dosage forms and are often used to predict in vivo performance. In vitro release studies were carried out for the formulations in both acidic and basic media to simulate in vivo conditions. The release studies were carried out at pH 1.2 (HCl buffer) (simulated gastric fluid) for 2 h, to mimic the acidic conditions prevailing in the stomach and for the next 22 h in basic medium, i.e., pH 6.8 (phosphate buffer), to mimic the environment in the small intestine. It was found that as the amount of HPMC K4M in the coating increased, there was a greater degree of hydration with simultaneous swelling. This would result in corresponding lengthening of the drug diffusion pathway and drug release rate. Drug release was generally linear for most of the formulations, especially formulation F9. Such linear release from tablet has been attributed to synchronization between swelling and erosion of the polymer in maintaining a constant gel layer.

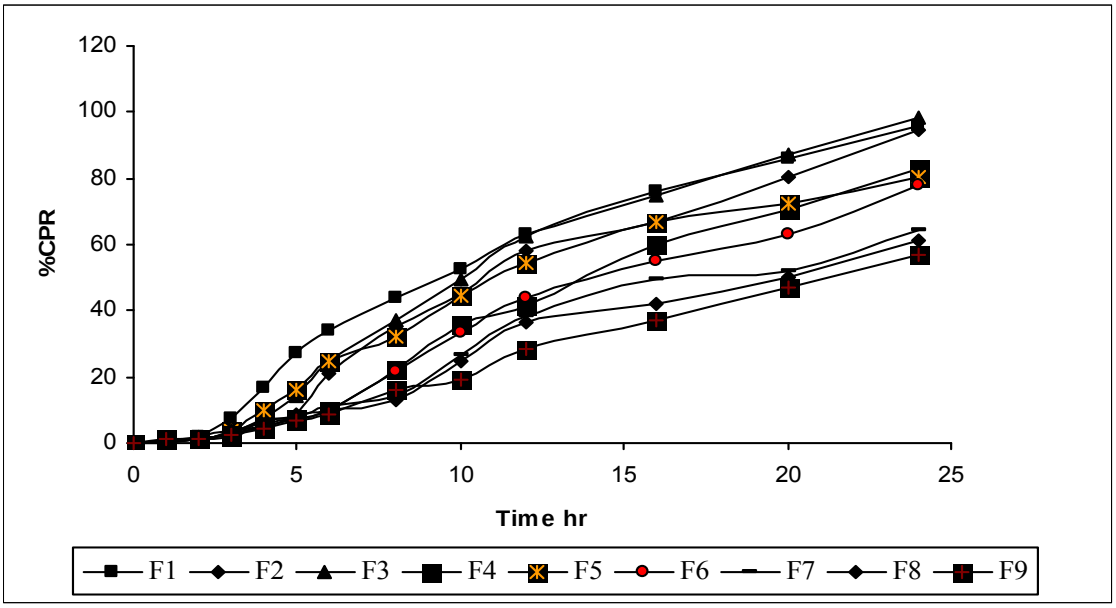

Fig.2*:* In *vitro* release profile of Propranolol hydrochloride from formulated compression coated tablets (Batch F1-F9)

Statistical analysis

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis carried out in Microsoft Excel 2003. The t_{10}, t_{90} values for the 9 batches (F1 to 9) showed a wide variation; the results are shown in Table 1.

The data clearly indicate that the values of t_{10}, t_{90}, are strongly dependent on the independent variables. The fitted Equations relating the response t_{10}, t_{90} to the transformed factor are shown in following Equations.

$$t_{10} = 3.748 + (1.137 * X_1) + (0.323 * X_2) - (0.105 * X_1X_2) + (0.0333 * X_1X_1) + (0.213 * X_2X_2$$

(Eq. 6)

(R square = 0.948)

$$t_{90} = 25.360 + (6.888 * X_1) + (1.178 *X_2) + (1.315 * X_1X_2) + (2.255 * X_1X_1) + (0.365 * X_2X_2)$$

(Eq. 7)

(R square = 0.985)

Table 4: Analysis of Variance For t_{10}:

	Df	***SS***	***MS***	***F***	***P***
Regression	5	8.517	1.703	2.445	0.046
Residual	3	2.090	0.697		
Total	8	10.606	1.326		

Table 5: Analysis of Variance for t_{90}					
	Df	***SS***	***MS***	***F***	***P***
Regression	5	310.379	62.076	39.551	0.006
Residual	3	4.709	1.570		
Total	8	315.088	38.386		

Multiple regression analysis of release rate constant showed that both the factors had statically significant with their quadratic terms ($p<0.05$). The values of the correlation coefficient indicate a goodness of fit. The polynomial Equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, (i.e. positive or negative).

Figure 3 and 4 showed the Counter plot of Amount of HPMC K4M (X_1) and amount of Ethyl cellulose (X_2) versus t_{10} *and* t_{90}, respectively. The plot was drawn using Sigma Plot Software 11.0 demonstration version. The data demonstrate that both X_1 and X_2 affect the in vitro drug release (t_{10} *and* t_{90}). The shaded area in the Figures 3 & 4 demonstrated the optimize area of the individual dependent variable (t_{10} *and* t_{90}). Figure 4 shows the overlapping counter plot of t_{10} and t_{90} which give optimize area for both dependent variable (t_{10} *and* t_{90}). It may also observed that the X_1(Amount of HPMC K4M) and X2 (amount of Ethyl cellulose) appear to favor the preparation of Propranolol HCl timed Controlled pulsatile release tablets. It can say that the drug release profile may be changed by appropriate selection of the X_1 and X_2 levels. The area in counter plot (Figure 4) shows if we selected X_1 and X_2 in this range we get the desired release profile of Propranolol HCl tablet.

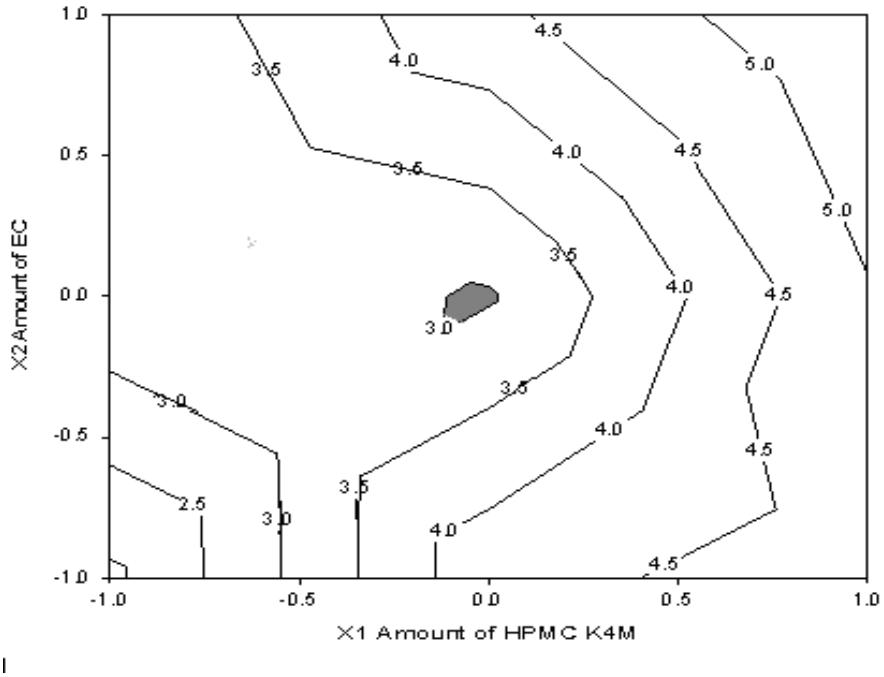

Fig. 3: Counter plot showing time require for 10% drug release (t_{10})

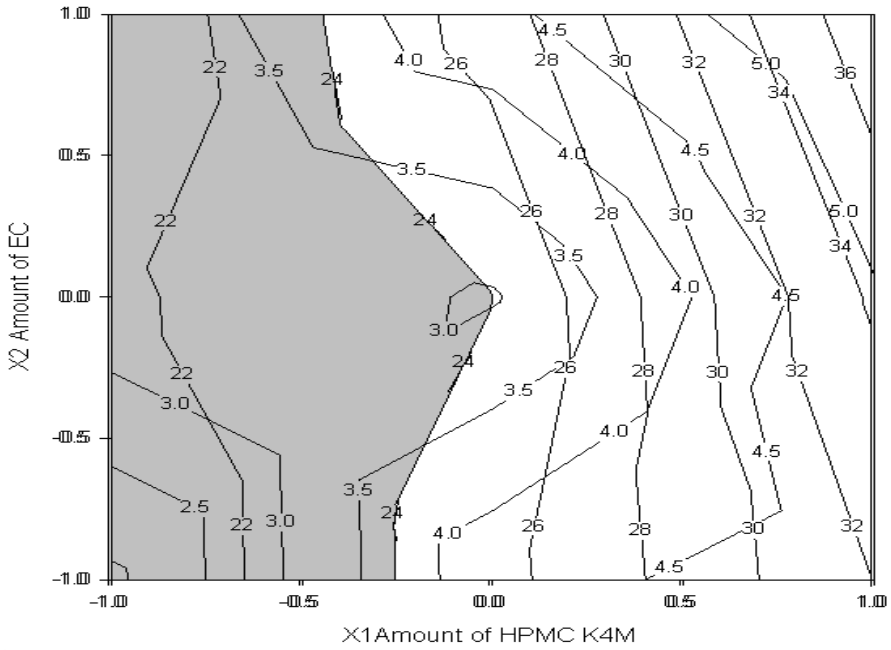

Fig. 4: Overlapping Counter plot showing time require for 10% *(t_{10}) and* 90% *(t_{90})* drug release

From the in vitro dissolution and statical analysis, Batch F3 (-1, 1) was selected as promising formulation and was found that formulation released the drug >90% in 24 hour.

Drug Release Kinetics study of optimize batch

The in vitro drug dissolution result of batch F3 was used for in various mathematical models (zero, first, Higuchi's square root, Hixson-Crowell cube root law and Peppas equation) to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined (Table 6).

Table 6: Results of model fitting of batch F3

	Intercept	Slope	R^2
Zero-order plot	-4.2398	4.6466	0.9707
First-order plot	+2.2084	-0.0652	0.8537
Higuchi plot	- 26.593	23.958	0.901
Hixson Crowell	+4.977	-0.141	0.9605
Korsmeyer–Peppas	-0.14	1.69(n)	0.9581

It was found that the in vitro drug release of optimize batch F3 was best explained by zero order as the plots showed the highest linearity (r^2 = 0.9707), Followed by Hixson Crowell model (r^2 = 0.9605), Korsmeyer–Peppas model (r^2 = 0.9581), Higuchi's model (r^2 = 0.901), and first order (r^2 = 0.8537). Drug release was also found to be close to zero-order kinetics, indicating that the concentration was nearly independent of drug release. The Hixson-Crowell plot (r^2 = 0.9605) indicated a change in surface

area and diameter of the tablets with the progressive dissolution of the tablet as a function of time. The corresponding plot (log cumulative percent drug release vs. log time) for the Korsmeyer-Peppas equation 5 indicated a good linearity (r^2 = 0.9581). The release exponent n was 1.69, which appears to indicate drug release rate was independent of time and controlled by a swelling mechanism it mean that follows Zero order drug release mechanism. Drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's kinetics). Kinetic models which fit zero order and Higuchi are more suitable for controlled release formulations.

CONCLUSION

The results of 3^2 full factorial design revealed that the independent factors *i.e.* amount of HPMC K4M (X_1) and amount of Ethyl cellulose (X_2) showed significant effect on the release of drug from the tablets. Results of multiple regression analysis indicated that low levels of X1 and a high level of X2 should be used to manufacture the tablet formulation with desired in lag time and in vitro dissolution. Formulation F3 was selected as promising formulation and was found that formulation released the drug >90% in 24 hour. From drug release kinetic study we can conclude that optimize batch F3 follows Zero order drug release mechanism.

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REFERENCES

1. H. Vogelpoel,* J. welink,* G.L. Amidon, H.E. Junginger, K.K. Midha, H. moller, M. Olling,* V.P. Shah,* D.M. Barends Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System (BCS) Literature Data: Verapamil Hydrochloride, Propranolol Hydrochloride, and Atenolol, Journal Of Pharmaceutical sciences,2004 ;93,8.
2. Lin SY, Lin KH, Li HL. "Hydrophilic excipients modulate the time lag of time controlled disintegrating press coated tablets." American Association of Pharmaceutical science Journal, 2004; 5 (4):54.
3. Sangalli ME, Maroni A., Foppoli A, Zema L, Giordano F, Gazzanig A. Different HPMC viscosity grades as coating agents for an oral time and/or site-controlled delivery system: a study on process parameters and in vitro performances, European Journal of Pharmaceutical Sciences.2004; 22:469–476.
4. Durig T, Skinner G, Hurcum W. "Ethyl cellulose in compression coated tablets: implications for time controlled pulsed release dosage forms." American Association of Pharmaceutical Scientists Annual Meeting, 2002; 10:14.
5. Lin SY, Lin KH, Li MJ. "Formulation design of double layer in the outer shell of dry coated tablet to modulate lag time and time controlled dissolution function: studies on Micronized Ethyl cellulose for dosage Form design (VII)." American Association of Pharmaceutical science Journal, 2004; 6 (3):17.

6. Pollock, D., and Sheskey, P., "Micronized Ethylcellulose: Opportunities in Direct-Compression Controlled-Release Tablets", Pharmaceutical Technology.1996, 20 (9), 120-130.
7. Hariharan M, Gupta. VK. "A novel Compression Coated Tablet Dosage From." Pharmaceutical Technology Year book 2001; 14-19.
8. Lachman L, Leiberman HA, Kanig JL. "The Theory and Practice of Industrial Pharmacy." Varghese publishing house, Bombay. 3rd Edition. 1990; 296.
9. Indian Pharmacopoeia. Government of India. Ministry of Health and Family Welfare. Delhi: Controller of Publication; 1996. p. 736.
10. The United States Pharmacopeia-30/National Formulary-25. Asian ed. Rockville MD: US Pharmacopoeial Convention, Inc; 2007. p. 3058.
11. Bourne DW. Pharmacokinetics. In: Banker GS, Rhodes CT, eds. Modern Pharmaceutics. 4th ed. New York, NY: Marcel Dekker Inc; 2002:67-92.
12. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963; 52:1145-1149.
13. Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation: I-theoretical consideration. Ind Eng Chem. 1931; 23:923-931.
14. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983; 15:25-35.