DEVELOPMENT OF PROPRANOLOL HYDROCHLORIDE MATRIX TABLETS: AN INVESTIGATION ON EFFECTS OF COMBINATION OF HYDROPHILIC AND HYDROPHOBIC MATRIX FORMERS USING MULTIPLE COMPARISON ANALYSIS

Madhusmruti Khandai *, Santanu Chakraborty, Anuradha Sharma, Debashisha Panda, Nazia Khanam, Santosh Kumar Panda
PG Department of Pharmaceutics, College of Pharmaceutical Sciences, Berhampur-760002, ORISSA.
*E Mail: santanu_nil@rediffmail.com

ABSTRACT

The aim of the present work was to develop sustain release matrix formulation of Propranolol hydrochloride and investigate the effects of both hydrophilic and hydrophobic polymers on *in-vitro* drug release. Matrix tablets were prepared by direct compression method using different concentration of Hydroxypropylmethylcellulose (HPMC) and Ethyl Cellulose (EC). Prepared formulations were subjected to various studies like hardness, friability, thickness, % drug content, weight variation, dynamics of water uptake and erosion etc. Tablets were subjected to *In-Vitro* drug release in 0.1 N HCl (pH 1.2) for first 2 hours followed by phosphate buffer (pH 6.8) for remaining hours. *In-vitro* drug release data were fitting to Higuchi and Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. It was observed that combination of both the polymers exhibited the best release profile and able to sustain the drug release for prolong period of time. Swelling study suggested that when the matrix tablets come in contact with the dissolution medium, they take up water and swells, forming a gel layer around the matrix and simultaneously erosion also takes place. FT-IR spectra revealed that there no interaction between drug and polymers. Multiple comparison analysis was confirmed that there exists a significant difference in the measured Higuchi rate constant and $t_{50\%}$ among the matrices. So the combination of both hydrophilic and hydrophobic polymers successfully employed for formulating the sustained release matrix tablets of propranolol hydrochloride.

Keywords*:* Propranolol hydrochloride, Diffusion, Erosion, Statistical analysis

INTRODUCTION

Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Sustained release dosage forms would be most applicable for drugs having short elimination half lives [1]. Propranolol hydrochloride (PRO-HCl), a nonselective beta-adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, phaeochromocytoma, cardiac arrhythmias [2] and many other cardiovascular disorders. PRO-HCl undergoes extensive and highly variable hepatic first-pass metabolism following oral administration, with a reported systemic bioavailability between 15% and 23% [3-4]. PRO-HCl has half-life of 3 to 5 hours so patients are routinely asked to take PRO-HCl for several times in a day. Such frequent drug administration may reduce patient's compliance and therapeutic efficacy. In recent years slow or sustained release formulations of PRO-HCl has become available with claims that these formulations maintain beta-adrenoreceptor blockade throughout a 24 hours period and enable the drug to be given once daily [5]. Propranolol Hydrochloride has a short elimination half-life, which makes it a suitable candidate to be delivered at a controlled rate. The most commonly used method of modulating the drug release is to include it in a matrix system [6]. Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance [7]. For the present research work hydroxypropyl methyl cellulose HPMC (K4M) and Ethyl Cellulose (EC) were used as matrix formers. Among the different hydrophilic polymers, cellulose ether polymers are the first choice, especially hydroxypropylmethylcellulose (HPMC), which has been extensively investigated for this purpose [8-9]. The drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers are essential to include in the matrix system [10], along with a hydrophilic matrix for developing sustained-release dosage forms. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels.

The objective of the present study was to develop controlled release matrix formulations of propranolol hydrochloride and to examine the effects of both hydrophilic and hydrophobic polymers on in-vitro drug release. In the present study, propranolol hydrochloride matrix formulations were prepared by using hydrophilic polymer, HPMC K4M and hydrophobic polymer, EC alone and in combination to study the release kinetics and find out the effects of both the polymers and their combinations.

MATERIALS AND METHODS

Materials

Propranolol Hydrochloride was a gift sample from Cipla Lab. Ltd., Mumbai. HPMC K4M, Ethyl cellulose (15cps) was procured from Genuine Chemicals, India. Microcrystalline Cellulose and talc were procured from Nice Chemicals, Nagpur. Other materials and solvents used were of analytical grade.

Preparation of tablets

All the formulations were prepared by direct compression method. The drug (80mg/tablet) and other excipients used in the formulations passed through a No. 60 sieve prior to compression. Powder blends were prepared using a cone mixer for 15 min. Then talc was added and mixed for another 5 min. The amount of polymers and others ingredients are given in Table 1. The required quantity of the ingredients for preparing the sustained release formulations were compressed using a single punch-tableting machine (Cadmach® Machinery Co. Pvt. Ltd., Mumbai) equipped with 6.5 mm circular, flat and plain punches. The batch size of each formulation was 100 tablets.

Table 1. Composition of Sustain Release Matrix Tablets of Propranolol hydrochloride (80 mg)*

Formulations	Ingredients (mg/tablet)				
	Propranolol HCl* (mg)	HPMC K4M* (mg)	Ethyl Cellulose* (mg)	MCC* (mg)	Talc* (mg)
F1	80	20	-	95	5
F2	80	40	-	75	5
F3	80	60	-	55	5
F4	80	-	20	95	5
F5	80	-	40	75	5
F6	80	-	60	55	5
F7	80	20	20	75	5

*Tablet weight: 200 mg.

Table 2. Properties of the Propranolol hydrochloride matrix Tablets

Formulations	Thickness* (mm)	Hardness** (kg/cm^2)	Friability+ (%)	Weight++ Variation (%)	% Drug*** content
F1	3.21 ± 0.21	4.9 ± 0.16	1.01 ± 0.32	3.115 ± 0.41	99.71 ± 1.43
F2	3.32 ± 0.16	5.8 ± 0.11	0.41 ± 0.08	2.402 ± 0.11	99.41 ± 2.70
F3	3.45 ± 0.46	5.4 ± 0.89	0.76 ± 0.03	1.346 ± 0.89	100.12 ± 1.11
F4	3.36 ± 0.13	5.2 ± 0.43	0.83 ± 0.10	2.118 ± 0.134	100.12 ± 2.40
F5	3.16 ± 0.09	5.6 ± 0.61	0.44 ± 0.11	2.153 ± 0.41	99.48 ± 1.61
F6	3.42 ± 0.31	5.5 ± 0.73	0.53 ± 0.03	2.361 ± 0.19	101.36 ± 0.98
F7	3.37 ± 0.19	5.2 ± 0.43	0.81 ± 0.02	2.119 ± 0.42	100.02 ± 0.84

Evaluation of matrix tablets

The quality control tests for the matrix tablets, such as hardness, friability, weight variation etc. were determined using reported procedure [11]. Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet from the average weight of tablet was calculated. Hardness was determined by taking 6 tablets from each formulation using a digital tablet hardness tester (Electro lab Ltd, Mumbai, India) and the average of pressure (kg cm^{-2}) applied for crushing the tablet was determined. Friability was determined by first weighing tablets equivalent to 6.5g after dedusting and placing them in a Roche® friabilator (Electrolab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dedusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. The thickness of the tablets was determined using a digital screw gauge (Mitutoyo, Japan). Five tablets from each batch were used, and average values were calculated (Table 2).

Drug content (Assay)

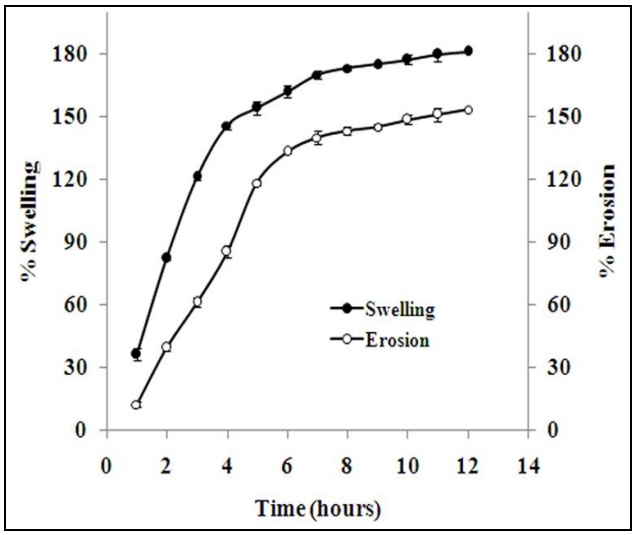
Ten tablets were finely powdered and an amount equivalent to 80 mg of propranolol hydrochloride was accurately weighed and transferred to a 100 ml volumetric flask and extracted with phosphate buffer (pH 6.8). The mixture was then filtered to remove the un-dissolve particle and 1 ml of the filtrate was suitably diluted and analyzed for propranolol hydrochloride content at 290 nm [12] using double beam UV/Visible spectrophotometer (UV-2450-Shimadzu Japan). This method was validated for linearity, precision and accuracy. Table 2 summarizes the data.

Swelling and erosion study

Swelling and erosion studies were performed using the method described by Reynold et al [13]. Weighed tablets (H_1) were taken on previously weighed watch glass and placed in a flat bottom dissolution vessel, containing phosphate buffer (pH 6.8) at 37^0 C. At one hourly time intervals (1-12 hours) tablets were withdrawn and excess amount of water was removed from the tablet by using blotting paper and weighed (H_3) on a single pan balance.

The wet tablets were dried in an oven at 110^0C for 24 hours then placed in desiccators and finally weighed as dry weight (H_2). The experiment was repeated three times for each individual time intervals. The swelling and erosion studies were carried out with stirring speed of 100 rpm (paddle type). The calculated results were given in Figure 1.

Figure 1 Swelling and Erosion behavior of optimized formulation of matrix tablet (formulation F7). Data are represented as mean ± SD, *n*=3)



The percent absorption (A) was calculated as (Swelling),

$$A\% = 100\left(\frac{H_2 - H_1}{H_1}\right) \quad (1)$$

The percent erosion (E) was calculated as,

$$E\% = 100\left(\frac{H_1 - H_2}{H_1}\right) \quad (2)$$

***In-Vitro* drug release Study**

Release of Propranolol Hydrochloride was determined using USP (XXI) six stage dissolution rate test apparatus I (Thermolab®) at 50 rpm. The dissolution rate was studied using 900 ml of 0.1 N Hydrochloride (pH 1.2) for first 2 hr followed by phosphate buffer (pH 6.8) for the remaining hours. The temperature was maintained at 37± 0.2^0C. Samples of 5 ml each were withdrawn at different time intervals i.e. 30, 60, 90,120,150,180 up to 720 min, filtered through Whatman filter paper (Auroco Pvt Ltd, Thailand) and replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and analyzed for propranolol hydrochloride content using double beam UV/Visible spectrophotometer (UV-2450-Shimadzu Japan) at 290 nm. The release studies were conducted in triplicate (Figure 2a and 2b).

Analysis of release profiles

The rate and mechanism of release of Propranolol Hydrochloride from the prepared matrix tablets were analyzed by fitting the dissolution data into the zero-order equation [14]

$$Q = k_0 t \quad (3)$$

where *Q* is the amount of drug released at time t and k_0 is the release rate constant.

First order equation [15]

$$ln\,(100-Q) = ln\,100 - k1t \quad (4)$$

where k_1 is the release rate constant.

The dissolution data was fitted to the Higuchi's equation [16]

$$Q = k_2 t^{1/2} \quad (5)$$

where k_2 is the diffusion rate constant.

Figure 2a Cumulative % Propranolol hydrochloride released *vs.* time (mean ± *SD*, *n* = 3) from formulations F1, F2, F3

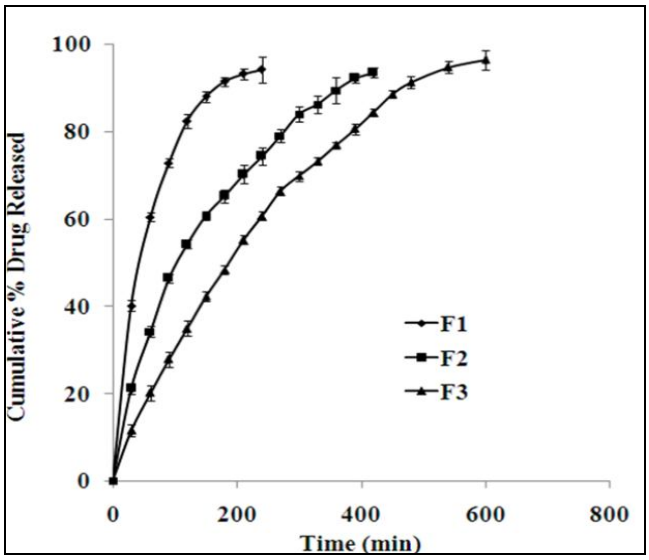
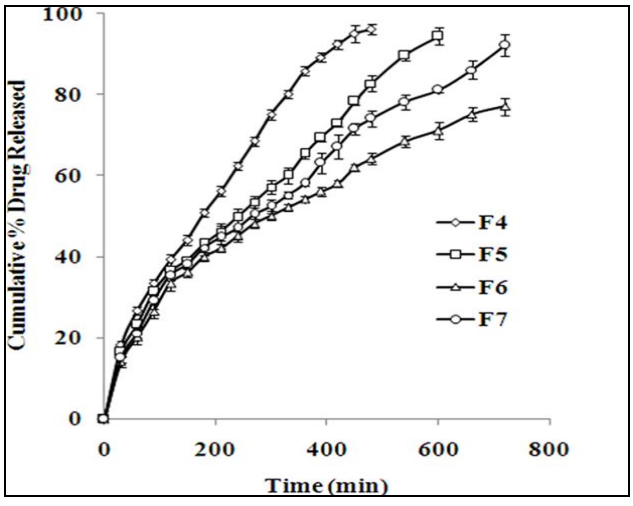


Figure 2b Cumulative % Propranolol hydrochloride released *vs.* time (mean ± *SD*, *n* = 3) from formulations F4, F5, F6, F7



To compare the dissolution profiles, several release models were tested, such as Higuchi's equation, which can provide information about drug particles dispersed in a

matrix. The drug release data was further analyzed by Peppas equation [17-18]

$$\frac{M_t}{M_\infty} = kt^n \qquad (6)$$

Where n = diffusional exponent, M_t = amount of drug released at time t, $M\infty$ = amount of drug released at time ∞, K is the kinetic constant.

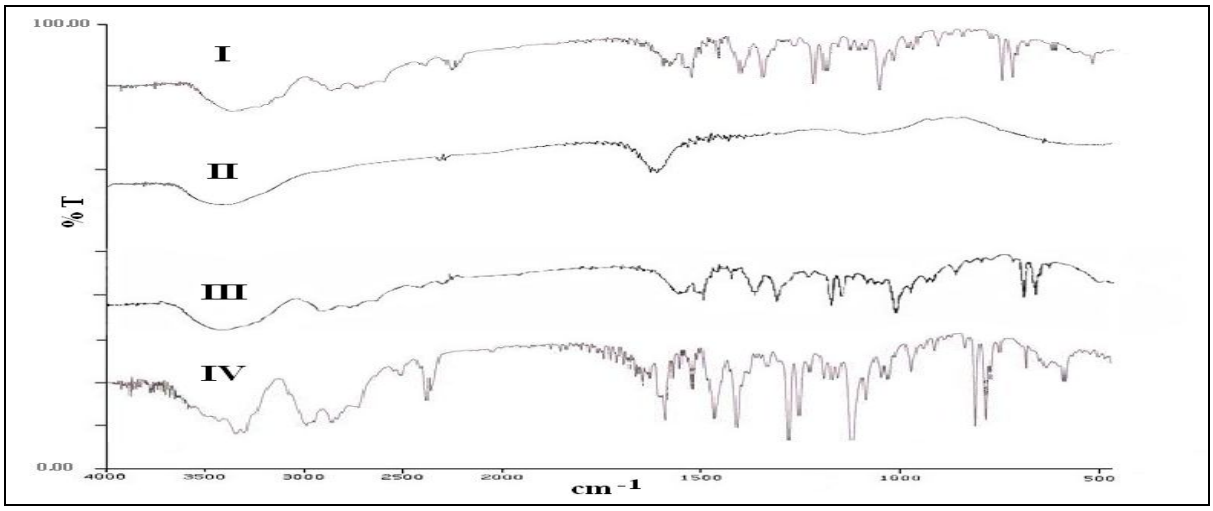
Thus M_t / $M\infty$ is the fraction of drug release at time t, a measure of the primary mechanism of the drug release and n characterizes the mechanism of drug release from the formulations during dissolution process (Table 3).

Table 3. Kinetics of Drug Release from Propranolol hydrochloride Matrix Tablets*

Formulations	Drug release kinetics, Coefficient of determination 'r²'			Korsmeyer Model	Higuchi rate constant (K_2)	Release exponent (n)	$t_{50\%}$ (hour)
	Zero Order	First Order	Higuchi Equation				
F1	0.961	0.913	0.962	0.995	6.278	0.575	0.73
F2	0.943	0.911	0.993	0.995	4.769	0.545	1.71
F3	0.916	0.814	0.984	0.999	4.510	0.537	3.21
F4	0.944	0.931	0.982	0.991	4.787	0.590	2.68
F5	0.899	0.809	0.980	0.986	3.885	0.665	3.63
F6	0.952	0.948	0.997	0.998	2.932	0.799	4.63
F7	0.937	0.924	0.991	0.997	3.465	0.540	4.04

* Analyzed by the regression coefficient method.

Figure 3 FT-IR spectra of pure Propranolol hydrochloride (I), HPMC (II), ethyl cellulose (III), and Optimized formulation F7 (IV).



Zero order, First order and Higuchi equation fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Peppas equation), which is often used to describe the drug release behavior from polymeric system.

FT-IR Study

Infrared spectrum was taken in the Perkin- Elmer FT-IR (spectrum RX) by scanning the optimized formulation in potassium bromide discs. The sample of pure drug (Propranolol HCl), pure polymers and the optimized formulation (F7) were scanned (Figure 3).

Statistical analysis

The data were presented as mean ± standard deviation. The drug release data was subjected to one way analysis of variance(one way ANOVA) followed by Holm-Sidak test for multiple comparison analysis ($p<0.05$) to find out whether significant difference was present between the formulations or not.

RESULTS AND DISCUSSION

Physical characterization of the tablets

All the formulations were prepared according to the formula given in Table 1. The prepared matrix tablets

were evaluated for various physical properties as indicated in Table 2. All the batches were produced under similar conditions to avoid processing variables. All the formulations were evaluated for various physical parameters such as weight variation, thickness, hardness, friability and drug content. Hardness of tablets ranged from 4.9 ± 0.16 to 5.8 ± 0.11 kg/cm^2, thickness of tablets were found within the range of 3.16 ± 0.09 to 3.45 ± 0.46 mm. The percentage friability of all the formulations was in between 0.41 ± 0.08 to 1.01 ± 0.32 percent. The values of hardness test and percent friability indicates good handling property of prepared tablets. The drug content uniformity in the tablets was within the range from 99.41 ± 2.70 to 101.36 ± 0.98 %.

***In-vitro* drug release studies**

The *in-vitro* drug release study was shown in Figure 2a and 2b. Results of one way ANOVA followed by Holm-Sidak test for multiple comparison analysis suggested a significant difference among the studied matrices for the measured responses (Higuchi rate constant and $t_{50\%}$). It was observed that the drug release was slower from formulations containing hydrophobic polymer ethyl cellulose as compared to hydrophilic HPMC polymer. This may be due to hydrophobic nature of ethyl cellulose, which restrict the penetration of medium in side the matrix and also restrict the formation of gel layer around the matrix as compared to the hydrophilic HPMC. When the polymer concentration was increase from 10 to 30% the drug release rate was found to decrease. This is due to the reason that the swelling degree is less because of higher concentration of polymers. But, further increase in concentration of the polymer did not significantly affect the drug release rate.

Formulation F1 and F4 containing 10% HPMC and 10% EC individually were able to sustain the drug release for 4 and 8 hours respectively (94.13 ± 2.98 for HPMC at 4 hours and 96.12 ± 1.37 for EC at 8 hours). In case of formulation F2, F3 containing 20% and 30% HPMC showed 93.46 ± 1.02% and 96.35 ± 2.29% drug released in 7 hours and 10 hours respectively.

Formulation F5, F6 containing 20% and 30% EC showed 94.39 ± 2.13% and 77.13 ± 2.11% drug released in 10 hours and 12 hours respectively. This again, is due to the hydrophobic nature of ethyl cellulose which restricts the formation of gel layer around the matrix formulation (Figure 2a and 2b) and retarded drug release from the matrix [19].

By increasing the HPMC and EC concentration more than 30% (up to 40%) of individual formulation, 95.11 ± 1.38% and 76.08 ± 2.74% drug was released in 10 hours and 12 hours respectively. Statistical analysis shows that there was no significant difference between the formulations containing 30% and 40% polymer. So, up to 30% polymer level was selected for the present study.

In case of formulation F7, where combination of both the hydrophilic and hydrophobic polymers were present at a low concentration (10% EC was incorporated with 10% HPMC), was able to sustain the drug release for 12 hours (92.16 ± 2.37% drug released in 12 hours). This may occur due to presence of both hydrophilic and hydrophobic polymer which allows little swelling but did not allow rapid diffusion of the drug from the matrix.

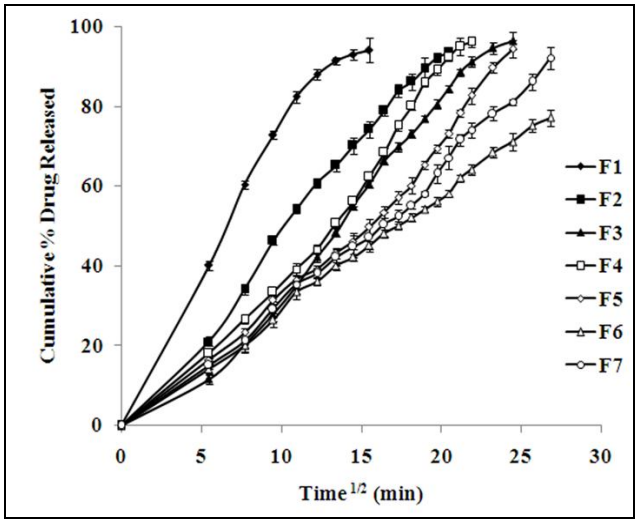
Simple visual observation of Figure 1 shows a swelling and erosion effect from F7 formulation. About 20 to 60% of the Propranolol hydrochloride was released within the first hour of dissolution study. This phenomenon may be attributed to surface erosion and initial disaggregation of the matrix tablet which occurs due to the formation of the gel layer around the tablet core [20]. In case of formulations F4, F5 and F6, only 20 to 26% drug was released due to the hydrophobic nature of the ethyl cellulose polymer. However in case of formulation F7 where hydrophilic and hydrophobic polymer combination was present no burst release was observed (only 21% drug release in 1 hour).

It is reported that if more than 30% drug is release in first hour of dissolution may indicate the chance of dose dumping [21]. So the formulations prepared without ethyl cellulose may have the probability of dose dumping. Therefore the formulations formulated using the combination of HPMC and EC did not show any burst release which indicated the reduced possibility of dose dumping.

The release kinetic data for all the formulations is shown in Table 3. The kinetic data of all the formulation showed good fit in Korsmeyer equation which indicated the combined effect of diffusion and erosion mechanism for controlled drug release. The value of release exponent 'n' was ranged from 0.537 to 0.799 (Table 3) which indicates non-Fickian mechanism of drug release.

Higuchi rate constant was found to decrease linearly with increase in either of the polymer concentration (Table 3, Figure 4). Through multiple comparison analysis by Holm-Sidak test it was confirmed that there exists a significant difference ($p<0.05$) in the measured Higuchi rate constant among the matrices.

Figure 4 Higuchi plot for cumulative percent Propranolol hydrochloride released *vs.* square root of time (mean ± SD, $n = 3$) from different formulations



No significant difference was observed for this measured response when the HPMC concentration was varied from 20% to 30%. Similar insignificant difference was observed when the data were compared between lowest concentration of EC (F4) and moderate to high concentration of HPMC (F2 & F3). The same statistical method was employed to study the existence of any significant difference among the formulations for the other response ($t_{50\%}$) and a significant difference was observed

Swelling and erosion study

The swelling (%) and erosion (%) was shown in Figure 1. It is observed that swelling and erosion were depending on function of time. It is clear that the matrices undergo both swelling and erosion at the same time after placing them in dissolution media. So, both swelling and erosion occurred simultaneously in the matrix which helps in constant release of the drug from the matrices [22]. Constant release, in such situations, occurs due to increase in diffusional path length owing to swelling compensated by continuous erosion of the matrix [23].

FT-IR Study

FT-IR study (Figure 3) suggested that there was no interaction between the pure drug, polymers and their combination used in the study.

CONCLUSION

Results of the present research work demonstrate that the combination of both hydrophilic and hydrophobic polymers successfully employed for formulating the sustained release matrix tablets of Propranolol hydrochloride. It is observed that 10% of each the polymer in combination was able to produce desire formulation which release more than 90% drug in 12 hours. The mechanism of drug release was observed the combined effect of diffusion and erosion for controlled drug release. So, combination of both hydrophilic and hydrophobic polymer was suitable to produce the matrix tablet rather than the using a single type of polymer.

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