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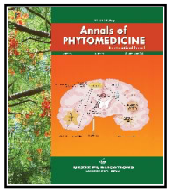

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Study the effect of polymers on the release rate of propranolol hydrochloride from controlled release matrix tablets

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Abstract

The aim of the present study was to see how polymers effect on the rate of propranolol hydrochloride (propranolol HCl) release from a controlled release matrix tablet. Hydroxy propyl methyl cellulose (HPKMC K4M and HPMC K15M) and ethyl cellulose (EC) were used to retard the rate of propranolol HCl release. The UV (Ultraviolet) absorption, FTIR (Fourier transform infrared) spectroscopy and DSC (Differential scanning calorimetry) spectra showed that propranolol HCl is compatible with HPMC K4M, HPMC K15M and ethyl cellulose. Controlled release tablets were made using a wet granulation technique. Angle of repose, bulk density, tapped density and compressibility index of propranolol HCl were all assessed prior to compression. Prepared tablets were evaluated for thickness, hardness, content uniformity, % friability and disintegration time and % drug release. All the parameters of pre-compression and post compression comply with standard specification. The *in vitro* drug release study disclosed that a formulation containing HPMC K15M and ethyl cellulose retarded the drug release rate for maximum time. The results of this investigation manifested that a blend of hydrophilic and hydrophobic polymers might be used to successfully enhance delayed rate of propranolol hydrochloride release from its controlled release matrix tablet.

1. Introduction

The primary objectives of controlled drug delivery system are to ensure safety, enhance efficacy of drug which improve patient compliance (Barzeh *et al.,* 2016; Ain *et al*., 2022). This could be affected by better modification and control of plasma drug level and reduction in dose frequency (Yassin *et al.,* 2021; Vyas and Khar 2006). Propranolol HCl is a class II antiarrhthmic drug which belongs to the beta-adrenergic blocking agents. It is extensively used as antihypertensive drug and is also used in treatment of angina pectoris, phaeochromocytoma, cardiac arrhythmias and many other cardiovascular disorders (Vidyadhara *et al.,* 2017; Gangireddy *et al.,* 2019). Propranolol hydrochloride is highly lipophilic drug (Soni *et al.,* 2021; Togaru *et al.,* 2017). It undergo extensive first pass metabolism, therefore its bioavailability is low approximately 30% (Huang *et al.,* 2004). Its elimination half-life is also low (3-5 h) which results in frequent dosing that decreases patient compliance (Alhmoud *et al.,* 2019). All the above reasons make it a model drug for controlled release dosage form (Mohapatra 2016). The matrix system is the most frequently used approach for controlling medication release (Shadbad *et al.,* 2011). Matrix system is very cost effective, flexible, broadly accepted method and its *in vitro* - *in vivo* correlation is good (Shojaee *et al.,* 2017; Ain *et al.*, 2016). A matrix system contains a medication that is uniformly dispersed and dissolved throughout a polymeric matrix, which are subsequently combined with other additives to create tablet dosage forms (Rebaz 2017; Ain *et al*., 2017). The polymeric matrix used acts as a release retardant and can be hydrophilic or hydrophobic polymers or different combinations of hydrophilic and hydrophobic polymers (Bala *et al.,* 2021; Chaiya and Phaechamud 2022). Polymeric material is the regulating component of drug delivery and it is a typical critical constituent in controlled release delivery systems (Antovska, 2017; Ain *et al.,* 2013). They are very cost effective, they have broad regulatory acceptance and are very flexible to provide desirable drug release profile desirable drug release profile (Khandai, 2010; Barzeh *et al.,* 2016). The use of hydrophilic polymer HPMC helps to regulate drug release by hydration of matrix (Hanbali *et al.,* 2018; Dhama *et al.,*2022) and including hydrophobic polymer, EC to retard the release rate (Patil *et al.,* 2016). In this research work, six formulations (F1, F2, F3, F4, F5, and F6) were prepared. F1 does not consist of any polymer, F2 was prepared by employing HPMC K4M, F3 was prepared by employing HPMC K15M, F4 was prepared by employing ethyl cellulose, F5 was prepared by employing HPMC K4M and ethyl cellulose and F6 was prepared by employing HPMC K15M and EC (Rowe *et al.,* 2004). Initially, possible incompatibilities between propranolol HCl and different polymers (HPMC K4M, HPMC K15M and ethyl cellulose) were determined by UV spectroscopy, DSC and FTIR. Angle of repose, bulk density, tapped density and compressibility index of propranolol HCl matrix tablet were investigated as pre-compression parameters. Post compression parameters like thickness, hardness, content uniformity, percent friability, disintegration time and percent drug release were evaluated on the prepared tablets.

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2. Materials and Methods

2.1 Materials

Propranolol hydrochloride was a gift sample from Ranbaxy, Gurugram. HPMC K4M, HPMC K15M and ethyl cellulose were purchased from Central Drug House (P) Ltd., New Delhi. The analytical grade excipients were obtained from Central Drug House (P) Ltd. in New Delhi.

2.2 Drug identification test

The melting point of drug was calculated by the capillary fusion method, using melting point equipment. The melting point that was discovered was written down and compared with values in Indian Pharmacopoeia 2007 (shown in Table 1). Pure drug can be identified by ultra violet spectroscopy. Maximum wavelength (λmax) of different concentrations of propranolol hydrochloride is recorded on a UV spectrophotometer (shown in Table 2). The samples were pulverized and completely mixed with potassium bromide, an infrared transparent matrix, at a ratio of 1:5 (Sample: KBr), respectively. The potassium bromide (KBr) discs were made by compressing the drug particles in a hydraulic press at a pressure of 5 tonnes for 5 min. Samples include pure propranolol HCl, HPMC K15M, HPMC K4M, ethyl cellulose and mixtures of propranolol HCl with HPMC K15M, HPMC K4M, and ethyl cellulose, respectively.

Table 1: Melting point of propranolol HCl

S.No.	Initial	Final
1	159	164
2	162	164
3	162	163
Average	161.00 ± 1.41	163.67 ± 0.47

Table 2: λmax of popranolol HCl solution

S.No.	Conc. of propranolol HCl	λmax
1	1 mg/µl	290 nm
2	1 mg/µl	290 nm
3	1 mg/µl	290 nm
4	1 mg/µl	290 nm
5	1 mg/µl	290 nm
6	Average	290 nm

2.3 Drug-polymer compatibility study

An examination of possible incompatibilities between an active medicinal ingredient and several excipients is part of the formulation stage of the development of a solid dosage form. Compatibility study was investigated by placing appropriated ratio of drug and polymer in normal condition and worst condition. Physical and chemical changes are noted using UV spectroscopy. Fourier transformer infrared spectrum (FTIR) and differential scanning calorimeter (DSC) are used to determine the possibility of a drug-excipient interaction.

2.4 Formulation of tablets

Tablets were prepared by wet granulation method as reported in Mulani *et al.* (2011), propranolol HCl (80 mg) was dry blended with appropriate quantity of polymer (s) and granulated using 1% w/v propanolic solution of polyvinyl pyrollidone (PVP-K30). A 12 No. sieve was used to filter the wet mass and it was further dried at 40ºC until the granules were completely dried. Finally, granules were sieved (18 No. sieve). These granules were blended with magnesium stearate and talc and compressed using single punch tableting machine, equipped with flat faced punch of 9 mm diameter. The formulation ingredients of various formulations are summarized in Table 3.

Table 3: Formulae of propranolol hydrochloride controlled release matrix tablets

S. No.	Ingredients (mg/tablet)	Formulation					
		F1	F2	F3	F4	F5	F6
1	Propranolol HCl	80	80	80	80	80	80
2	HPMC K4M	-	100	-	-	50	-
3	HPMC K15M	-	-	100	-	-	50
4	Ethyl cellulose	-	-	-	100	50	50
5	Microcrystalline cellulose	40	40	40	40	40	40
6	Talc	5	5	5	5	5	5
7	Magnesium stearate	5	5	5	5	5	5
8	Di-calcium phosphate	170	70	70	70	70	70
	Weight of the tablet	300	300	300	300	300	300

2.5 Evaluation of matrix tablets

2.5.1 Pre-compression parameters

Flowability is an important feature of bulk powders. The term "flowable" refers to an irreversible deformation of a powder that causes it to flow when external energy or force is applied. Powder flowability is expressed using a variety of factors such as angle of repose, carr's index and hausner ratio (Moondra *et al.,* 2018). Angle of repose is a sign of the frictional forces existing between particles. It had been determined by funnel method. In a funnel, a precisely weighed powder blend was placed. The funnel's height was modified so that the funnel's tip merely brushes against the apex of a heap of powder. The powders were allowed to freely flow out of the funnel onto a clean surface. The angle of repose was estimated after measuring the diameter of the powder cone. According to USP, the flow property is graded as excellent if the value of angle of repose is between 25 and 30°. The bulk density of a powder is the weight to volume ratio of an untouched powder sample, including the contribution of interparticulate void volume. As a result, both the density of powder particles and the spatial arrangement of particles in the powder bed influence bulk density. The tapped density was calculated by repeatedly tapping a powder sample in a graduated measuring cylinder or vessel. After the initial powder volume or weight was noted. The measuring cylinder or vessel was mechanically tapped, and volume or weight readings were taken until further volume or weight change was noticed. Tapped density was calculated by utilizing the standard tapping method using measuring cylinder. The compressibility index and hausner ratio are both indicators of a powder's ability to be compressed. The cylinder method was used to determine bulk density, tapped density, and carr's index (CI) was evaluated using the following equation:

$$CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

2.5.2 Post-compression parameters

The thickness of the individual tablet was measured with a screw gauge. 5 tablets of each batch were taken to evaluate tablet hardness with the monsanto hardness tester.

Another measure of tablet strength is its friability. Twenty tablets were weighed and placed in a roche friabilator, which were then operated for 100 revolutions (Ravi *et al.,* 2008). After that, the tablets were dusted and reweighed:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

For weight variation 20 tablets were weighed and the average weight was determined, from this individual deviation was measured (Lachman *et al.,*1990). Content uniformity was calculated by accurately weighing 20 tablets and crushed in a mortar; 300 mg of powder was taken into a 100 ml volumetric flask and made volume to 100 ml with demineralized (DM) water. The resulting solutions were sonicated and filtered. 1 ml of the filtrate was diluted to 100 ml volumetric flask with DM water. The absorbance of resulting solution was measured by using UV spectrophotometer at max 290 nm. The following formula was used to calculate the drug content in the formulation (Badshah *et al.,* 2010):

$$\text{Drug content} = \frac{\text{Conc.} \times \text{D.F.} \times \text{Amount of drug taken}}{1000}$$

Using disintegration apparatus, six tablets from each formulation were tested for disintegration. Use 0.1N hydrochloric acid as the immersion fluid. Run the machine for 2 h and check the state of the tablets. There should be no signs of disintegration or breaks on any tablet that could allow the contents to escape. Phosphate buffer solution of pH 6.8 can be used to replace the acid. Examine the status of the tablets after 60 min of operation.

2.6 *In vitro* dissolution studies

The USP (XXI) six stage dissolution rate test equipment was used to measure the release rate of propranolol hydrochloride at 50 rpm. To assess the dissolution rate, 900 ml of 0.1N hydrochloride (pH 1.2) was used for the first 2 h, followed by phosphate buffer (pH 6.8) for the remaining hours. The temperature was kept constant at 37.20°C. At various time intervals, 5 ml samples were taken and replaced with an equal volume of fresh dissolving medium. A spectrophotometer was used to examine the samples at a wavelength of 290 nm. The amount of drug release was calculated from the standard curve. All of the experiments were performed thrice. This procedure was done for each formulation separately (Kuksal, 2006; Ain *et al.,* 2017).

3. Results

3.1 Drug identification test

Melting point of propranolol hydrochloride was found to be 161 to 163°C. The melting point readings are depicted in Table 2. The observed value of λmax was found to be 290 nm which comply with standard specification. The values of λmax are shown in Table 3. The IR spectra of propranolol hydrochloride is characterized by its peaks at 1577 cm^{-1} (N-H Bend), 1240 cm^{-1} (C-O Str), 1157 cm^{-1} (C-N Str) and 1107 cm^{-1} (C-O-C Str). This shows that propranolol HCl is in pure form as all its peaks are presented in Figure 1.

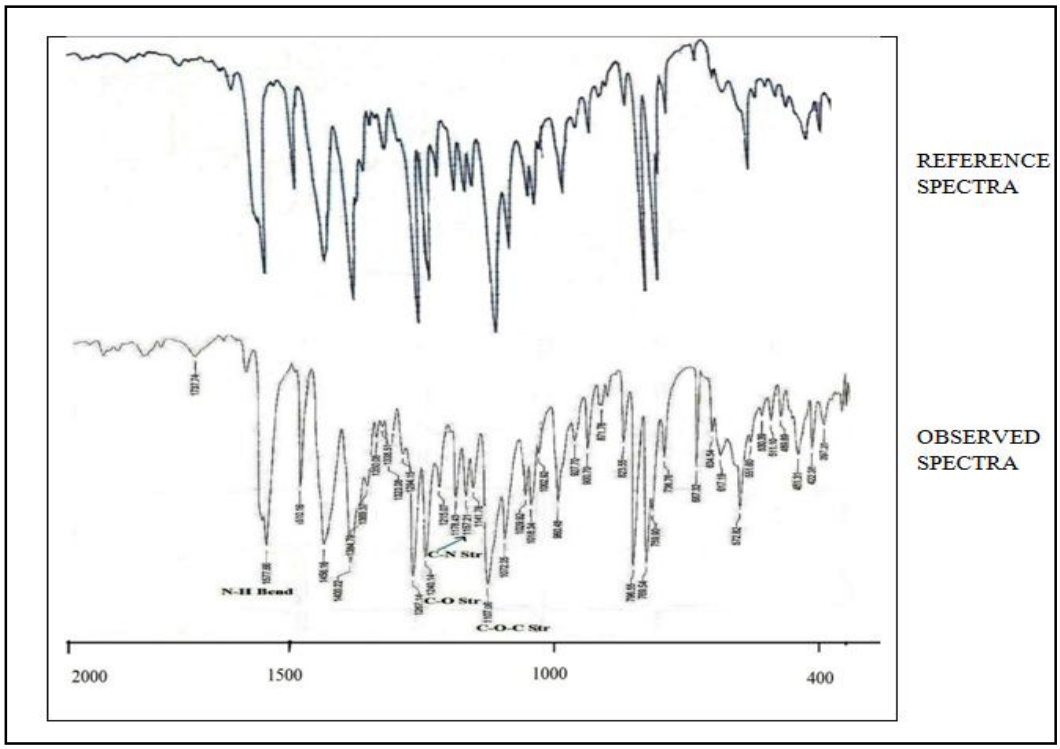

Figure 1: Comparison of FTIR spectra of pure drug (propranolol HCl) with reference spectra (IP 2007).

3.2 Drug-polymer compatibility study

Compatibility study was investigated by placing appropriate ratio of drug and polymer in normal condition and worst condition. Table 4 depicts the physical changes and chemical changes after 7 and 15 days. The result found that there was no physical changes such as discoloration, caking and liquefaction of in the physical mixtures at the end of the 7 and 15 days and the chemical changes was determined by absorption maxima (λmax) by UV spectroscopy. The result revealed that negligible change in the λmax scan at 290 nm. The result confirmed the absence of any interaction between propranolol HCl and polymers (HPMC K15M, HPMC K4M, and ethyl cellulose) in normal and worst condition.

Table 4 : Physical and chemical changes during drug-polymer compatibility study

Mixtures	7 days				15 days			
	Physical changes			Chemical changes	Physical changes			Chemical changes
	D	C	L	λmax	D	C	L	λmax
M1	-	-	-	290 nm	-	-	-	290 nm
M2	-	-	-	290 nm	-	-	-	290 nm
M3	-	-	-	290 nm	-	-	-	290 nm
M'1	-	-	-	290 nm	-	-	-	290 nm
M'2	-	-	-	290 nm	-	-	-	290 nm
M'3	-	-	-	290 nm	-	-	-	290 nm

D: Discoloration, C: Caking, L: Liquefaction.

M1, M2, M3: Mixtures of drug with HPMC K15M, HPMC K4M, Ethyl cellulose in normal condition.

M'1, M'2, M'3: Mixtures of drug with HPMC K15M, HPMC K4M, ethyl cellulose in worst condition.

3.2.1 Infrared spectroscopy

The FTIR spectras of propranolol HCl, HPMC K4M, HPMC K15M, and ethyl cellulose, popranolol HCl with HPMC K4M, HPMC K15M and ethyl cellulose respectively are shown in Figure 2. The peak due to N-H Str, O-H Str, C-H Str, N-H Bend, C-N Str, C-O Str and C-O-C Str are present in spectras of propranolol HCl with HPMC K4M, HPMC K15M and ethyl cellulose, respectively. This demonstrates that the drug and the polymer have no interaction.

3.2.2 DSC (Differential scanning calorimeter)

The DSC curve of pure propranolol hydrochloride showed only one endothermic response, which corresponded to the drug melting. Onset of melting was noted at 164.24°C with a corresponding heat of fusion (HF) of 116.1 J/g (Figure 3), whereas the melting endothermic peak of the drug in combination with polymers (HPMC K15M and ethyl cellulose) was found to be 162.77°C in a DSC thermogram presented in Figure 3. This shows that propranolol HCl does not interact with any of the polymer.

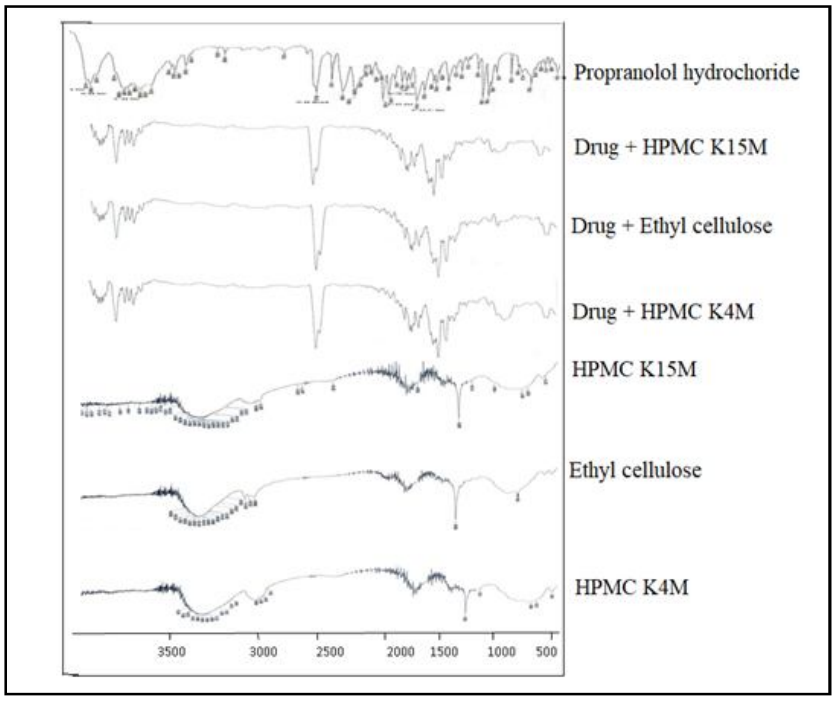

Figure 2: FTIR spectra shows drug-polymer compatibility.

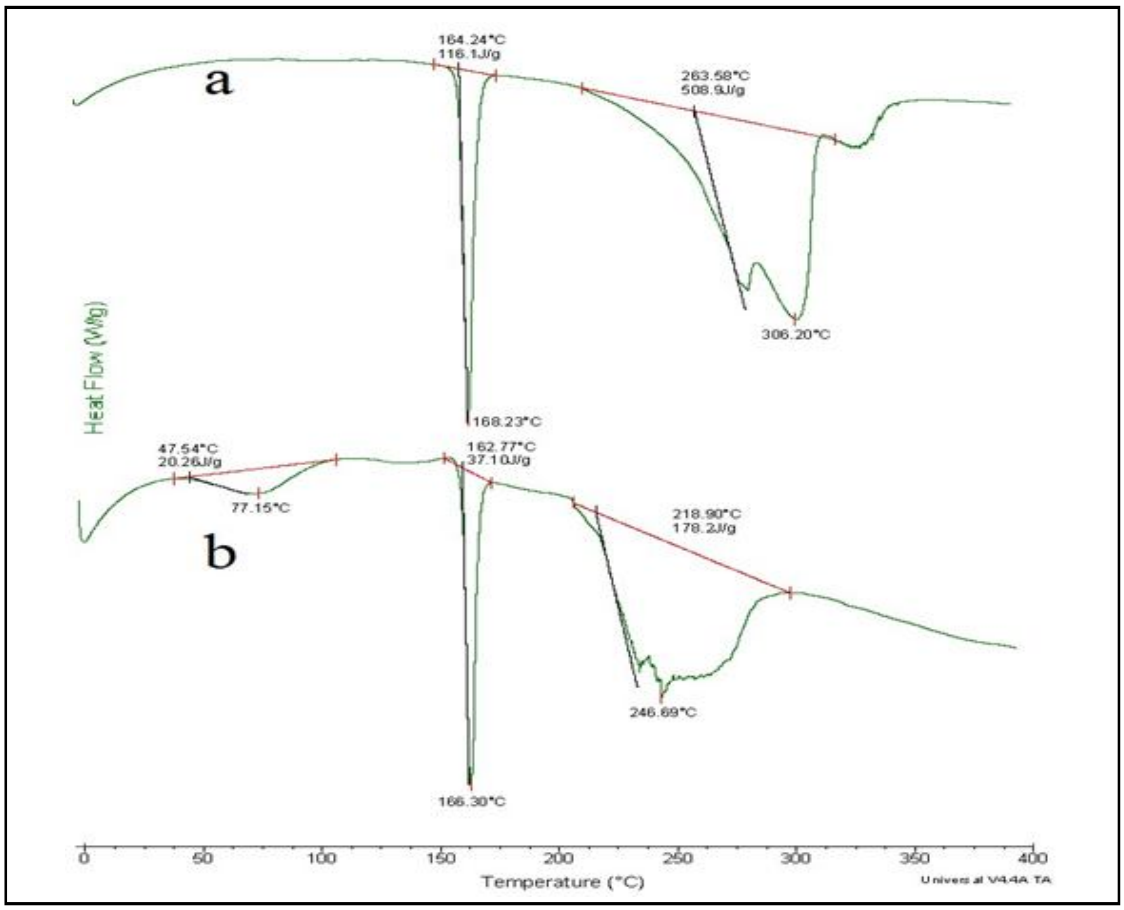

Figure 3: DSC spectra shows drug-polymer compatibility (a) DSC curve of pure propranolol hydrochloride. (b) DSC curve of propranolol HCl with HPMC K15M and ethyl cellulose.

Table 5: Pre-compression parameters of propranolol HCl

Formulation	Bulk density	Tapped density	Compressibility index (%)	Angle of repose (°)
F1	0.331	0.357	7.32	21.20
F2	0.326	0.337	3.51	19.17
F3	0.340	0.357	4.76	20.24
F4	0.333	0.350	4.99	19.57
F5	0.326	0.342	4.81	19.70
F6	0.330	0.350	6.31	20.92

Table 6: Post-compression parameters of propranolol HCl

Formulation	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Weight variation (mg)	Disintegration time %	Drug content
F1	4.2 ± 0.10	5.9 ± 0.65	0.60 ± 0.15	301 ± 5	6 min	98.76 ± 4.49
F2	4.4 ± 0.09	6.0 ± 0.33	0.49 ± 0.13	304 ± 9	Non disintegrating	93.22 ± 4.78
F3	4.1 ± 0.05	5.4 ± 0.27	0.76 ± 0.15	303 ± 9	Non disintegrating	97.37 ± 2.59
F4	4.3 ± 0.18	5.5 ± 0.19	0.38 ± 0.20	302 ± 6	Non disintegrating	95.50 ± 4.21
F5	4.3 ± 0.07	6.2 ± 0.34	0.60 ± 0.08	302 ± 6	Non disintegrating	98.80 ± 2.54
F6	4.2 ± 0.08	5.9 ± 0.22	0.49 ± 0.13	298 ± 8	Non disintegrating	98.52 ± 7.88

3.3 Pre-compression parameters

The results of the bulk density, tapped density, compressibility index and angle of repose are given in Table 5. All of the test product samples met the official requirements of compressibility index and angle of repose standards.

3.4 Post-compression parameters

The results of the uniformity of weight, hardness, drug content and friability of the tablets are given in Table 6. The average thickness of all tablets is 4.2 - 4.4 mm. The results of hardness reveals that F5 formulation showed the highest crushing strength value, however all the formulation has an almost similar hardness. The data obtained from these tests reveals that all pass the requirements for friability. The matrix tablets' low friability suggests that they are compact and hard. F2, F3, F4, F5, and F6 have been discovered to be non-disintegrating in both acidic (pH 1.2) and alkaline (pH 6.8) fluids, making them appropriate for oral controlled release. Disintegration time for F1 was 6 min. The reason behind it is that it does not contain any release retarding polymer therefore its disintegration time is less. The USP limits for the drug content of propranolol HCl in extended release tablets or capsules are set in a range between 90 - 110% of label, the result obtained in this studied show that all formulations found to be close to 100% of the label claim for propranolol in all formulations.

3.4.1 *In vitro* dissolution studies

In vitro dissolution studies were conducted on three tablets of each of the formulations such as F1, F2, F3, F4, F5 and F6. Table 7 shows the mean cumulative percent of propranolol hydrochloride release rate at various time intervals for each formulation. Amount of drug release at different time interval is shown in Figure 4. Using a combination of HPMC K15M and ethyl cellulose, the release rate of propranolol hydrochloride was extended up to 24 h.

Table 7: Percentage drug release of propranolol HCl at different time intervals

S.No.	Time (h)	% Drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	½	96.24 ± 2.2	13.54 ± 0.17	11.76 ± 0.45	11.83 ± 1.25	10.63 ± 0.87	8.76 ± 0.35
3	1	100.23 ± 0.27	22.98 ± 0.64	13.89 ± 1.45	19.03 ± 1.11	12.06 ± 2.15	11.35 ± 0.87
4	2	100.23 ± 0.27	27.27 ± 0.83	25.37 ± 1.69	28.30 ± 0.84	24.70 ± 1.51	22.25 ± 0.87
5	4	100.23 ± 0.27	50.78 ± 1.35	47.52 ± 1.05	52.67 ± 0.87	44.97 ± 0.48	40.63 ± 1.28
6	8	100.23 ± 0.27	78.91 ± 0.64	73.42 ± 1.06	81.14 ± 0.87	64.50 ± 1.75	59.18 ± 1.59
7	14	100.23 ± 0.27	96.41 ± 1.35	95.10 ± 2.22	100.01 ± 0.65	82.69 ± 1.05	70.33 ± 1.05
8	24	100.23 ± 0.27	99.98 ± 0.26	99.96 ± 1.50	100.53 ± 0.24	95.56 ± 0.48	91.61 ± 1.26

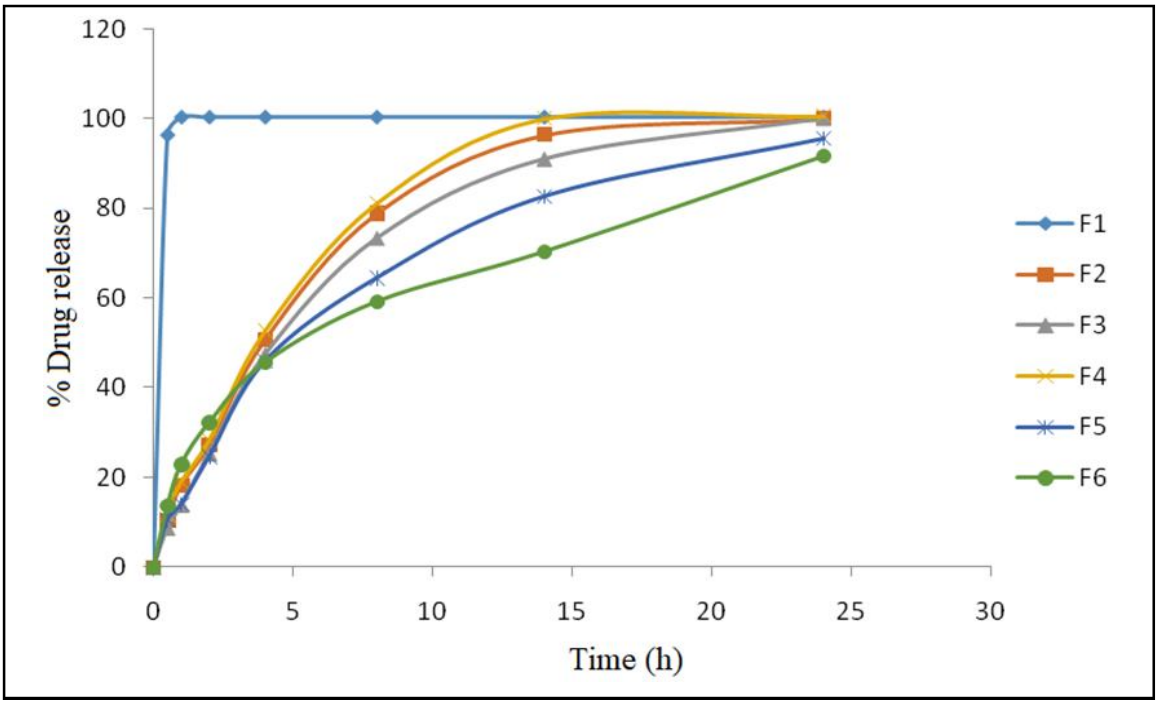

Figure 4: Effect of polymer on the % drug release of propranolol HCl controlled release matrix tablet.

4. Discussion

The present work was undertaken to formulate and evaluate controlled release matrix tablet of propranolol HCl using six different combinations of hydrophilic and hydrophobic polymers. As propranolol HCl undergo extensive first pass metabolism, therefore, its bioavailability is low and its elimination half-life is also low. Which results in frequent dosing that decreases patient compliance. Because of above mentioned reasons it is a model drug for controlled release dosage form. Initially drug identification tests were performed; namely, melting point, UV spectroscopy and FTIR. The result complies with the standard specification. Possible physical and chemical incompatibilities between an active drug substance and different excipients were done using UV spectroscopy, FTIR and DSC. The results are shown in Table 4, Figures 2 and 3. Table 4 shows that the polymers are compatible with propranolol HCl in normal and worst conditions. In Figures 2 and 3 additional peaks in spectra were identified due to polymers. The spectras of FTIR and DSC indicates drug is compatible with polymers.

The results of the angle of repose (<30) suggest that the powder has good flow characteristics. Lower carr's index values backed up this theory. Six formulations with different combination of polymers as shown in Table 1, were prepared using wet granulation method. The post compression parameters like uniformity of weight, hardness, drug content and friability of the tablets are given in Table 6. The data obtained from these tests reveal that all parameters are in acceptable limits. According to the drug content results, all formulations were determined to be near to 100 percent of the label claim for propranolol HCl in all formulations. Disintegration time for F1 was 6 min. else all other are non-disintegrating. The reason behind it is that it does not contain any release retarding polymer therefore its disintegration time is less as shown in Table 5. In F1 formulation 100 % of the drug released within first 2 h. with no evidence of sustained release. This is due to absence of any release rate retarding polymer in F1 formulation.

In formulations F2 and F3, containing HPMC K4M and HPMC K15M initial release rate of drug in 1 h was 23% and 13% to release rate in 8 h was 79% and 73%. The reason behind the decreased release rate of F3 as compared to F2 is that the release rate of an HPMC matrix type tablet is known to be strongly reliant on the viscosity grades and particle size of the HPMC polymer, which determine the tablet's swelling and erosion. The breakdown of HPMC particles with a high viscosity takes longer (lag time) to produce a gel layer, resulting in a slower release rate (Lee *et al.,* 1999). In F4 formulation only hydrophobic polymer was present therefore 100 % of drug was release within 14 h.

Formulation F5 and F6 containing HPMC K4M and K15M with EC show decrease in release rate as compared to F2, F3 and F4. The release rate of propranolol HCl in 1 h was reduced to 12% and 11% in F5 and F6 formulation, respectively. Further, the release rate of F6 formulation was 91% in 24 h, which is slowest among all formulations. The mechanism of drug release from the hydrophilic matrix was most likely owing to faster dissolution of the highly water-soluble core drug and its diffusion out of the matrix, producing pores for solvent molecules to enter. The incorporation of ethyl cellulose was observed to restrict drug, which might be due to decreased solvent penetration in the presence of a hydrophobic polymer, resulting in less drug diffusion from the matrix.

5. Conclusion

The findings of this study revealed that a combination of hydrophilic and hydrophobic polymers might be employed successfully to make a propranolol HCl controlled-release matrix tablet. The *in vitro* drug release study revealed that a formulation containing HPMC K15M and ethyl cellulose retarded the drug release for maximum time. 91.61 % drug was released after 24 h. F1 was the formulation which does not consist of any polymer, it released 100% drug within 1 h.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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