

# Design and Evaluation of Sustained Release Bilayer Matrix Tablets of Propranolol Hydrochloride

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## ABSTRACT

The purpose of the present study is to achieve suitable propranolol HCl therapeutic profile by formulating bi-layer tablet consisting of an immediate and a sustained release layer using hydrophilic polymers such as HPMC K15M and PEO 1105 as release rate retarding agents. The effect of concentration of hydrophilic matrix polymers HPMC K15M, PEO 1105 on drug release profile was studied. The formulations have shown an initial burst release to initiate the effect of loading dose and then followed by sustained release for 12 h from the controlled release layer. FT-IR studies proved the compatibility between the drug and polymers used in the study. The optimized formulation F9 (containing 40% of polymer HPMC K15M) gave propranolol release close to the theoretical CR release and was used to develop a bilayer matrix tablet of propranolol HCl. To determine the pattern of drug release, *in-vitro* release data was fitted into various release kinetic models like zero order, First order, Higuchi, and Peppas. The values indicated the non-fickian or anomalous transport with slow erosion of the polymer matrix followed by diffusion of drug resulted in linear drug release over a prolonged period of time.

**KEY WORDS:** Propranolol hydrochloride, Bilayer tablets, Direct compression, HPMCK15M.

## 1. INTRODUCTION

In conventional dosage forms, there may be no control over the drug release due to repetitive dosing which results in unpredictable and often toxic plasma concentrations, leading to major side effects. In addition bioavailability in case of conventional dosage forms may alter, based on factors such as physiochemical properties of the drug, excipients, various physiological factors. Controlled drug delivery system (CDDS) possess several advantages over conventional dosage forms like predictable and reproducible release rates, prolonged action especially for short half-life drugs, reduced toxicity, increased bioavailability of the drug due to localized activity (Divya, 2011). But CDDS failed to achieve these advantages due to dose dumping or burst release and failed to attain site specific drug delivery.

These factors led to the development of bilayer tablets to maintain sustained release of drug from the formulations. Bilayer tablet consists of two layers, one layer is composed of initial dose (immediate release layer) and other layer consists of maintenance dose (sustained release layer). Bilayer tablets can be formulated using a single drug or combination of drugs (incompatible drugs) (Shiyani, 2008). The pharmacokinetic data depends on initial burst release from immediate release layer, which results in sudden raise of drug concentration in systemic circulation. Later the drug level is maintained at steady state due to the delayed release of drug from the controlled release layer.

In the present research Propranolol hydrochloride (HCl) was selected for the development of bilayer matrix tablet which is a non-selective beta-adrenergic blocker and it is commonly used to treat hypertension, angina pectoris, pheochromocytoma and cardiac arrhythmias (Niranjan Patra, 2007). It is completely absorbed upon oral administration. Due to its short plasma half-life propranolol HCl is taken as daily doses, i.e once every 6 to 8h this repetitive dosing may lead to toxicity due to improper elimination of drug (Sherlin, 1983). In recent years, sustained release formulations of propranolol HCl became available so that these formulations maintain  $\beta$  adreno- receptor blockade for about 24 h and reduce the drug dosing (Taylan B *et al* 1966). The objective of this study is to achieve suitable therapeutic profile for propranolol HCl by formulating a bi-layer tablet consisting of an immediate and a controlled release layer using hydrophilic materials such as HPMC K15M and PEO 1105 as release rate retarding agents.

## 2. MATERIALS AND METHODS

**Materials:** Propranolol hydrochloride was a gift sample obtained from Life Line formulations, Vijayawada. Poly ethylene oxide WSR 1105 and HPMC K15M were purchased from Colorcon Asia Pvt. Ltd. Micro crystalline cellulose (MCC), Sodium starch glycolate (SSG), Magnesium stearate, Talc and Methanol were purchased from SD Fine Chemicals, Ltd, Mumbai. Other materials and solvents used were of analytical grade.

### Methods:

#### Compatibility studies:

**Fourier Transform Infrared Spectroscopy (FTIR) study:** (Nirav D. Solanki, 2013) Drug – excipient interactions play a major role in the drug release from dosage form. Parkin Elimer Fourier transform infrared spectroscopy (FTIR)

has been used to study the physical and chemical interactions between drug and the excipients used. The pellets were prepared by KBr-press method and the spectra were recorded over the wave number range of 4000 to 500nm.

**Preparation of propranolol hydrochloride bilayer tablets:** (Harika Rayakala, 2010) Drug and excipients were accurately weighed according to formulae given in table.1 & 2. The bilayer tablets of propranolol HCl were prepared by Direct Compression method.

**Table.1. Formulation of Immediate release layer**

S.No	Ingredients (mg/tablet)	Formulations		
		IR 1	IR 2	IR 3
1	Propranolol Hydrochloride	25	25	25
2	Sodium Starch Glycolate	10	15	20
3	Micro Crystalline Cellulose	155	150	145
4	Magnesium Stearate	5	5	5
5	Talc	5	5	5
	<b>Total weight</b>	<b>200</b>	<b>200</b>	<b>200</b>

**Table.2. Formulation of the Controlled release layer**

S.No	Ingredients(mg/tab)	Formulations									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Propranolol HCl	55	55	55	55	55	55	55	55	55	55
2	Poly Ethylene Oxide WSR 1105	25	50	75	100	125	-	-	-	-	-
3	Hydroxyl Propyl Methyl Cellulose K15M	-	-	-	-	-	25	50	75	100	125
4	Micro Crystalline Cellulose	160	135	110	85	60	160	135	110	85	60
5	Magnesium Stearate	5	5	5	5	5	5	5	5	5	5
6	Talc	5	5	5	5	5	5	5	5	5	5
	<b>Total weight</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>

**Formulation of Immediate release layer:** The dose in the formulation for the immediate release layer was 25mg and the maintenance dose (55mg) of Propranolol HCl was calculated. The composition of the immediate release (IR) layer was given in Table.1. Propranolol HCl, sodium starch glycolate and microcrystalline cellulose were passed through a mesh (1150 $\mu$ m) and blended in a polythene bag for 15 minutes. The blend was mixed with talc and magnesium stearate for 2 minutes and kept in desiccator until further use.

**Formulation of the sustained release layer:** The composition of the controlled release (CR) layer is given in Table-2. Drug and excipients were accurately weighed and added into the polythene bag and was blended for 20 minutes to achieve uniform distribution of the drug in formulation.

**Compression of Bilayer tablets:** The required quantity of ingredients for the controlled release layer was compressed using a single punch tableting machine (Cadmach, Kolkata, India) equipped with 8mm circular, flat and plain punches. Over this compressed layer, the required quantity of the IR layer was placed and compressed to obtain hardness in the range of 4-5kg/cm<sup>2</sup> to form a bilayer matrix tablet.

#### **Evaluation of bilayer tablets:**

**Pre-compression evaluation** (Patrick J Sinko, 2006): The powder blend was evaluated for pre-compression properties like angle of repose, bulk density, tapped density, carr's index, hausner's ratio.

**Post compression evaluation** (Leon Lachman, 2013): The compressed tablets were evaluated for thickness, diameter, weight variation, hardness friability and disintegration time.

**Weight variation:** According to I.P. 20 tablets were weighed individually which were randomly selected for the determination of weight variation. The mean and standard deviation were determined.

**Hardness:** It was determined by using Monsanto hardness tester (Shreeji Chemicals, Mumbai) and the average pressure of (kg/cm<sup>2</sup>) applied for crushing the tablet was determined.

**Friability:** It was determined by first weighing 10 tablets and placing them in Roche Friabilator (Campbell Electronics), which was rotated for 100 revolutions at 25rpm. After dusting, the total remaining mass of the tablets was recorded and the percent friability was calculated.

**Drug content uniformity:** Ten tablets were taken and powdered. The amount equivalent to 100mg of propranolol was accurately weighed and transferred to 100ml volumetric flask. To this 70ml of buffer (0.1 N HCL) was added and shaken for 10min and finally volume was made upto mark with buffer. The obtained solution was then filtered by using Whatman filter paper (No.41) and 1 mL of the filtrate was suitably diluted upto 100 mL with buffer solution and analysed for Propranolol HCl content at 290nm using a double beam UV/Visible spectrophotometer and 0.1N HCl as blank.

**Disintegration test:** The different formulas of IR layer were compressed alone at the same compression force and their disintegration times were compared with the reference conventional tablet (Propranolol 25mg). The disintegration time was determined by using 0.1 N HCL (pH 1.2).

**In-vitro dissolution studies:** The release rate of Propranolol HCl bilayer tablets was determined by using Dissolution testing apparatus IP type I (Paddle type). The dissolution testing was performed using 900 mL of 0.1 N HCl at  $37 \pm 0.5^\circ\text{C}$  temperature and speed 100 rpm. The 5 mL samples were taken at regular time intervals of 15, 30, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660, 720 minutes and replacement of buffer was done for each sample to maintain sink conditions. The samples were filtered through Whatman filter paper (No. 41). Dissolution studies were carried out for initial 2 hours in 0.1 N HCl, then with pH 6.8 phosphate buffer for next 10 hours and absorbance was measured at 290nm using UV/Visible spectrophotometer.

**In vitro drug release characterization models:**

**Zero order release kinetics:** Zero order release kinetics describes the process of constant drug release. In simplest form, zero order release can be represented as  $Q = Q_0 + K_0t$

Where,  $Q$  = the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves),  $Q_0$  = the initial amount of drug in solution (it is usually zero), and  $K_0$  = the zero order release constant. The plot made: cumulative % drug release vs. Time (zero order kinetic model) (Venkata srikanth Meka, 2012).

**First order release kinetics:** Dissolution rate can be expressed by the equation which was proposed by Noyes and Whitney as:  $-dc / dt = k (C_s - C_t)$

Where,  $dc / dt$  is the rate of change in concentration with respect to Time and  $k$  is the rate constant.

The integrated form of the equation is:  $\ln [C_s / (C_s - C_t)] = kt$

$$\log C = \log C_0 - kt / 2.303$$

Where,  $C_0$  is the initial concentration of drug and  $K$  is first order constant.

The equation in resemblance with other rate law equations, predicts a first order release which depends on the concentration gradient.

**Higuchi Model:** Higuchi describes the drug release from an insoluble matrix as the square root of a Time-dependent process based on Fickian diffusion.

$$Q_t = [2DS' (A - 0.5S')]^{0.5} \cdot t^{0.5}$$

Simplifying,

$$Q_t = kH (t)^{0.5}$$

Where,  $Q_t$  is the amount of drug released in Time  $t$ ,  $D$  is the diffusion coefficient,  $S$  is the solubility of drug in the dissolution medium,  $A$  is the drug content per cubic centimeter of matrix tablet, and  $KH$  is the release rate constant for the Higuchi model (Higuchi, 1963)

**Korsmeyer-Peppas Model:** Korsmeyer derived a simple relationship to describe drug release from a polymeric system, which was obtained by fitting first 60% drug release data was fitted in Korsmeyer-Peppas model:

$$M_t / M_N = K t^n$$

Where,  $M_t / M_N$  is fraction of drug released at Time  $t$ , and  $k$  is the rate constant and  $n$  is the release exponent. The  $n$  value is used to characterize different release mechanisms as given in table for cylindrical shaped matrices (Peppas NA 1985).

**Swelling studies** (Ramana, 2012): Bilayered tablets were weighed individually ( $W_1$ ) and placed separately in 1.2pH buffer containing petri dish plates and incubated at  $37 \pm 0.10^\circ\text{C}$ . The tablet was taken from the petri dish and excess water from the surface was removed by using filter paper. The swollen tablet was then reweighed ( $W_2$ ), and the swelling index (SI) or percent hydration was calculated using the following formula

$$\% \text{ of hydration} = (W_2 - W_1) \times 100 / W_2$$

Where,  $W_1$  - initial weight of tablet,  $W_2$  - weight of tablet at time.

**Similarity Factor** (Hosna Banu, 2011): The similarity factor ( $f_2$ ) was used to compare the dissolution profile of each formulation with that of the marketed formulation. In this approach, recommended by the FDA guidance for the industry, when the value is between 50 and 100, the two profiles nearly identical. The value is determined by the following equation,

$$f_2 = 50 + \log \{ [1 + (1/n) t = 1 \times n (R_t - T_t)] \times 100 \}$$

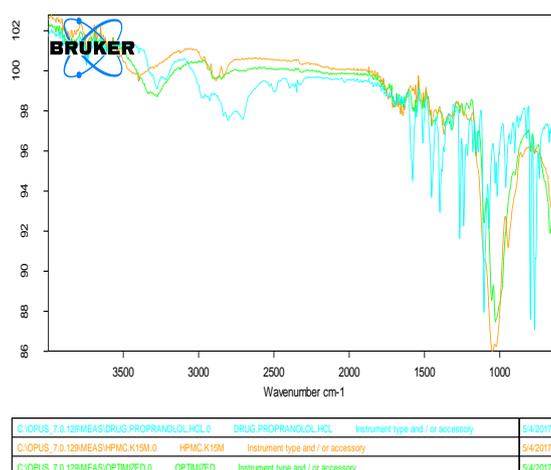
Where,  $n$  is the number of dissolution time points,  $R_t$  and  $T$  are the reference and test dissolution values at time.

### 3. RESULTS AND DISCUSSION

**Compatibility studies by FTIR:** Bilayer tablet of HPMC K15M based formulation showed all the characteristic peaks of propranolol HCl with minor shifts in its FTIR spectrum. It indicates that principal peaks of bilayer tablet matches to that of pure drug Propranolol Hydrochloride. This proves the compatibility between the drug and the excipients used in this investigation.

**Pre-formulation studies:** The bulk density of various formulations ranged between 0.33 and 0.39 gm/ml and tapped density between 0.43 gm/ml to 0.45 gm/ml which indicates good packing character. The values obtained for angle of repose for F1-F5 and F6-F10 were in the range of  $29^{\circ}.8'$  to  $25^{\circ}.9'$  &  $28^{\circ}.6'$  to  $25^{\circ}.9'$ . This indicates good flow property of the powder blend. Compressibility index was in the range between 11.36% to 10.16% indicating that the powder blends have good flow property.

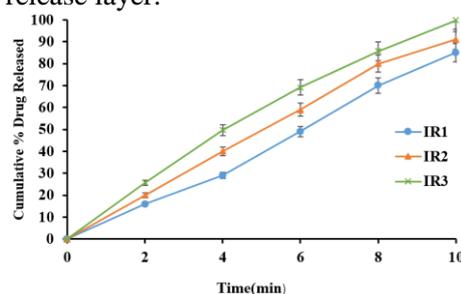
**Post-compressional studies:** Bilayer tablet of propranolol HCl was prepared by direct compression method. The entire batch of tablets passed weight variation test as the percentage weight variation was within the pharmacopoeial specified limits. The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets from each batch were in the range of  $4.35 \pm 0.02$  kg/cm<sup>2</sup>. The percentage friability of all formulations were within the range of 0.13-0.15 $\pm$ 0.05%. The drug content uniformity in bilayer tablets was 101.3% $\pm$ 0.4.



**Figure.1. FT-IR Overlay of Pure drug, HPMC K15M, bilayer Tablet**

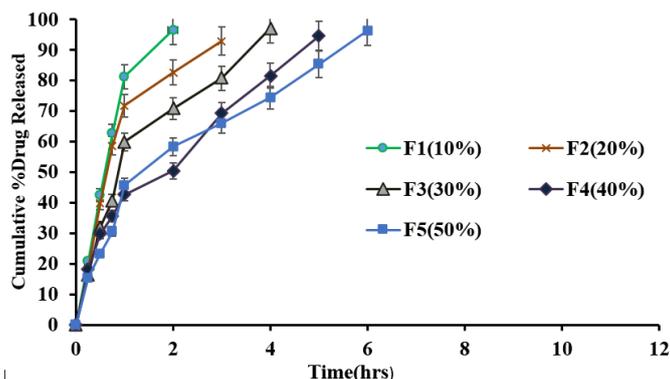
#### ***In-vitro* dissolution:**

***In-vitro* Dissolution Profile of IR Layer Formulations:** Based on the results, the cumulative % drug release for IR1, IR2 and IR3 formulations at the end of 10 minutes were found to be  $85.92 \pm 1.23$ ,  $91.12 \pm 0.22$  and  $99.72 \pm 1.37$  respectively. The *in vitro* Drug release profiles for IR1, IR2 & IR3 are given in Figure-2. The results depict that the maximum amount of drug was released from the Formulation IR3 when compared to other formulations IR1 and IR2. This is due to more concentration of super disintegrant (SSG) in the formulation. Hence Formulation IR3 was confirmed as an optimized immediate release layer.



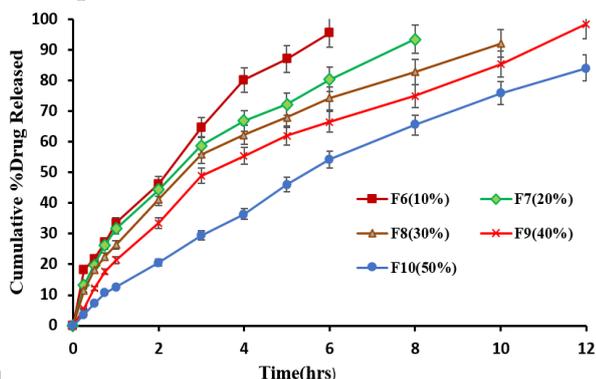
**Figure.2. *In-vitro* drug profile for IR Layer of Propranolol HCl (IR1-IR3)**

***In-vitro* Dissolution Profile of CR Layer Formulations:** Propranolol HCl release from CR layer of matrix tablets were studied in medium 1.2 pH acidic buffer for initial 2hrs followed by 6.8 pH buffer for remaining 10 hrs. Based on the results it was found that more than 99% drug was released within 2hrs in the case of formulation F1 (containing 10% of PEO 1105). Further proportion of the polymer (PEO) increased to 20-50% in the formulations, the release process of Propranolol HCl decreased to some extent (F2-F5). As the proportion of PEO increased, the release process of Propranolol HCl decreased, but the formulations F1-F5 are failed to develop a controlled release matrix system over 12 hrs of time period. This is may be due to absence of sufficient PEO gel barrier around the surface of tablet and high water solubility of the drug. So the formulations F1 to F5 were failed to control the drug release from the matrix system. The *in vitro* Drug release profiles for F1-F5 were given in Figure 3.

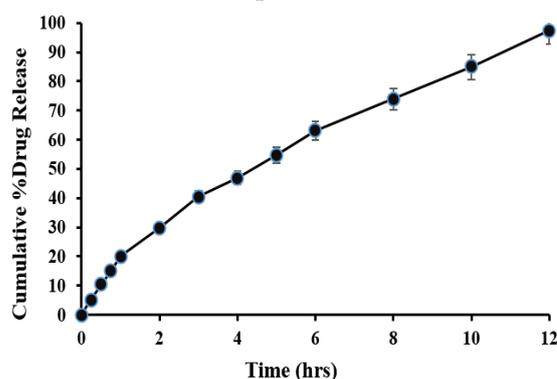


**Figure.3. In-vitro drug release profile of Propranolol HCl CR layer prepared by using various concentrations of PEO WSR 1105 (F1-F5)**

Formulations (F6 to F10) showed the initial burst release of Propranolol HCl which is due to rapid dissolution of the highly hydrophilic drug from the superficial layers of immediate release layer. F9 showed controlled drug release up to 12 hours which is nearly identical to the release profile of marketed formulation. The percent drug release for F9 at the end of 12 hrs was found to be 98.41%. F10 showed less release over 12 hours, due to increase in the concentration of HPMC K15M in the formulation, resulted in a decreased drug release rate. F9 (containing 40% of polymer HPMC K15M) gave propranolol release close to the theoretical CR release. Hence F9 was selected as an optimized formula of controlled release layer to develop a bilayer matrix tablet of propranolol HCl. The *in vitro* Drug release profiles of CR Layer (F6-F10) and bilayer tablets are given in Figures 4 & 5. The optimized formulation was compared with the marketed formulation which have shown the similar release profiles.



**Figure.4. In vitro drug release profile of Propranolol HCl CR layer prepared by using various concentrations of HPMCK15M (F6-F10)**



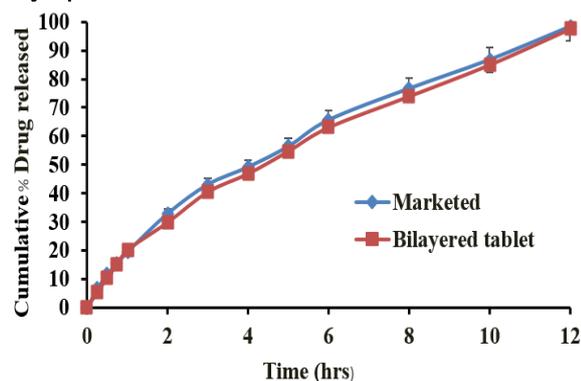
**Figure.5. In vitro drug release profile of Propranolol HCl Bilayer matrix tablets**

**In vitro drug release characterization models:** To determine the mechanism of drug release, *in-vitro* release data was fitted into various release kinetic models like zero order, First order, Higuchi and Peppas. The corresponding release rate constants were calculated and given in Table.3. Regression coefficients ( $R^2$ ) obtained for the first order kinetics were found to be superior when compared with those of zero order kinetics, which indicates the drug release from formulations followed the first order kinetics. Higuchi's plot for prepared bilayer matrix tablets were found to be linear which indicates diffusion controlled drug release. To estimate the drug release pattern of formulations the obtained *in-vitro* data was fitted into Korsmeyer peppas equation which explains the transport mechanism. The value of release exponent ( $n$ ) for all the formulations F6-F10 and bilayer tablets were in between 0.51 to 0.58 and 0.62 indicates the anomalous transport with slow erosion of the polymer matrix followed by diffusion of drug resulted in linear drug release over a prolonged period of time.

**Table.3. In-Vitro Drug Release Kinetics of bilayer Tablet**

Zero order constant mg/hr		First order constant ( $hr^{-1}$ )		Higuchi constant ( $mg/hr^{1/2}$ )		Peppas Constant	
$K^0$	$R^2$	$K^1$	$R^2$	KH	$R^2$	$R^2$	"n"
17.472	0.932	0.201	0.975	64.334	0.987	0.991	0.622

**Swelling Index:** In the present study, the percentage water uptake of the formulations (F6-F9) ranged from 109 to 136 %. The % water uptake was found to be increased upon increasing the concentration of HPMC K15 M in the formulations and hence, the water uptake capacity increases. The diffusion of the drug from the polymer depends on the water uptake capacity of the tablet. The swelling study indicated that the rate of swelling was proportional to the polymer content. The maximum swelling index was found in formulation F9, containing a higher proportion of k15M, and the lowest in F6. The swelling index profile of Formulations F6-F9 is depicted in Fig no 7.



**Figure.6. Comparison of *In-vitro* drug release profile of bilayer matrix tablet with Marketed Formulation**

**Similarity factor:** It was calculated in order to compare the release profile of bilayer tablet with the marketed formulation. Formulation F9 showed ( $f_2$ ) value greater than 50 indicating similar release profiles with that of marketed product. As the value of ( $f_2$ ) was found to be 60.5 for F9. The optimized formulation F9 is comparable with the marketed formulation.

#### 4. CONCLUSION

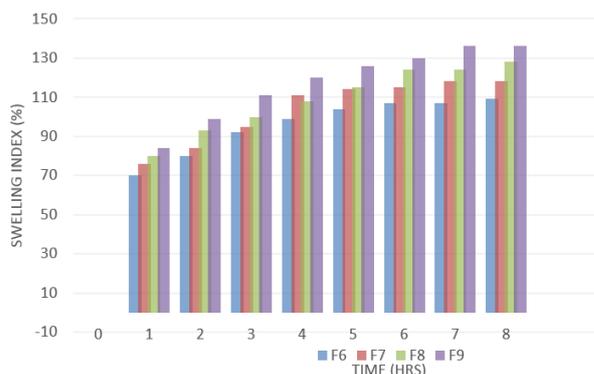
In this present study propranolol HCl was formulated as controlled release bilayer matrix tablets by using PEO 1105 and HPMC K15M polymers in the CR layer. Hence it can conclude that formulated bilayer tablets of Propranolol HCl were developed successfully with IR layer comprising of SSG and CR layer comprising of HPMC K15M as retardant polymer by Direct Compression method and able to provide the drug release over a prolonged period of time i.e. 12hrs. Developed formulation is expected to reduce the frequency of administration there by reduces the chance of adverse effects associated with frequently administered propranolol HCl tablets.

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**Figure.7. Swelling index profile of Propranolol HCl Bilayer matrix tablets prepared by using various concentrations of HPMCK15M (F6-F9)**

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