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FORMULATION AND *IN VITRO* EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF PROPRANOLOL

Pamu Snehalatha*[1], Mr. Dr.D.Venkata Ramana [1], Mrs. Pravalika [1]

[1]Department of Pharmaceutics, Holy Mary Institute of Technology and Science (College of pharmacy), Keesara - Bogaram - Ghatkesar Rd, Kondapur, Telangana 501301.

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Abstract:

The present study involves in the formulation and evaluation of Controlled release tablets of Propranolol (10mg). The objective of the present study was to formulate Propranolol Controlled release tablets by direct compression method by using Eudragit S 100, HPMC K4 M and HPMC K15 M. MCC was used as diluting agent, Magnesium stearate was used as a lubricant and Talc was used as a glident. This Controlled release the drug up to 12 hours in predetermined rate. The formulated powder blend was evaluated for bulk density, tapped density, compressibility index and angle of repose. The formulated tablets were evaluated for physical characteristics of Controlled release tablets such as thickness, hardness, friability, weight variation and drug content. The results of the formulations found to be within the limits specified in official books. The tablets were evaluated for In-vitro drug release studies by using USP type II dissolution test apparatus. The dissolution test was performed in 0.1 N HCL for 2 hr and phosphate buffer pH 6.8 for 12hrs. The in-vitro cumulative drug release profile of all formulations F1-F12 hours showed good drug release. Hence, Formulation F7 was the most promising formulation as it gives satisfactory release (98.29 %) for 12 hours and F7 found to be the best formulation.

Keywords: *Propranolol, Eudragit S 100, HPMC K4 M, HPMC K15 M and Controlled release tablets.*

Corresponding author:

Pamu snehalatha,

Department of Pharmaceutics,
Holy Mary Institute of Technology and Science,
Kondapur, Telangana, Email Id- snehapamu522@gmail.com

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INTRODUCTION:

Drug delivery is a technique of delivering medication to a patient in such a manner that specifically increases the drug concentration in some parts of the body as compared to others. The ultimate goal of any delivery system is to extend, confine and target the drug in the diseased tissue with a protected interaction. Every Dosage form is a combination of drug/active pharmaceutical ingredients (APIs) and the non-drug component called excipients/additives. APIs are the actual chemical components used to treat diseases. [1]

Administration of drugs into the body cavities (rectal, vaginal) can be impractical and unfeasible as they can be degraded at the site of administration (e.g., low pH in the stomach) and may cause local irritations or injury when the drug concentration is high at the site of administration. Some APIs are sensitive to the environment and can benefit from reducing the exposure to environmental factors (light, moisture, temperature and pH), or they need to be chemically stabilized due to the inherent chemical instability. APIs mostly have unpleasant organoleptic qualities (taste, smell and compliance), which reduce patient compliance. [2,3] The glidants prevent lump formation by reducing the friction between particles and improve the flowability of the tablet granules or powder. Anti-adherents stop the powder from sticking to the machines during manufacturing. Lubricants ensure the smooth surface of dosage form, by reducing the friction between the walls of the tablets and the die cavity during ejection. Flavouring agents help to mask the unpleasant odour and colourants are added to aid in recognition and aesthetics. [4] The most common dosage forms comprise tablets, capsules, pills, ointments, syrups and injections. Various routes of drug administration are tabulated in Table 1 and Figure 3. The preferred route of drug administration depends on three main factors: The part of the body being treated, the way the drug works within the body and the solubility and permeability of the drug. For example, certain drugs are prone to destruction by stomach acids after oral administration resulting in poor bioavailability. Hence, they need to be given by the parenteral route instead. Intravenous administration of drugs gives 100% bioavailability. [5]

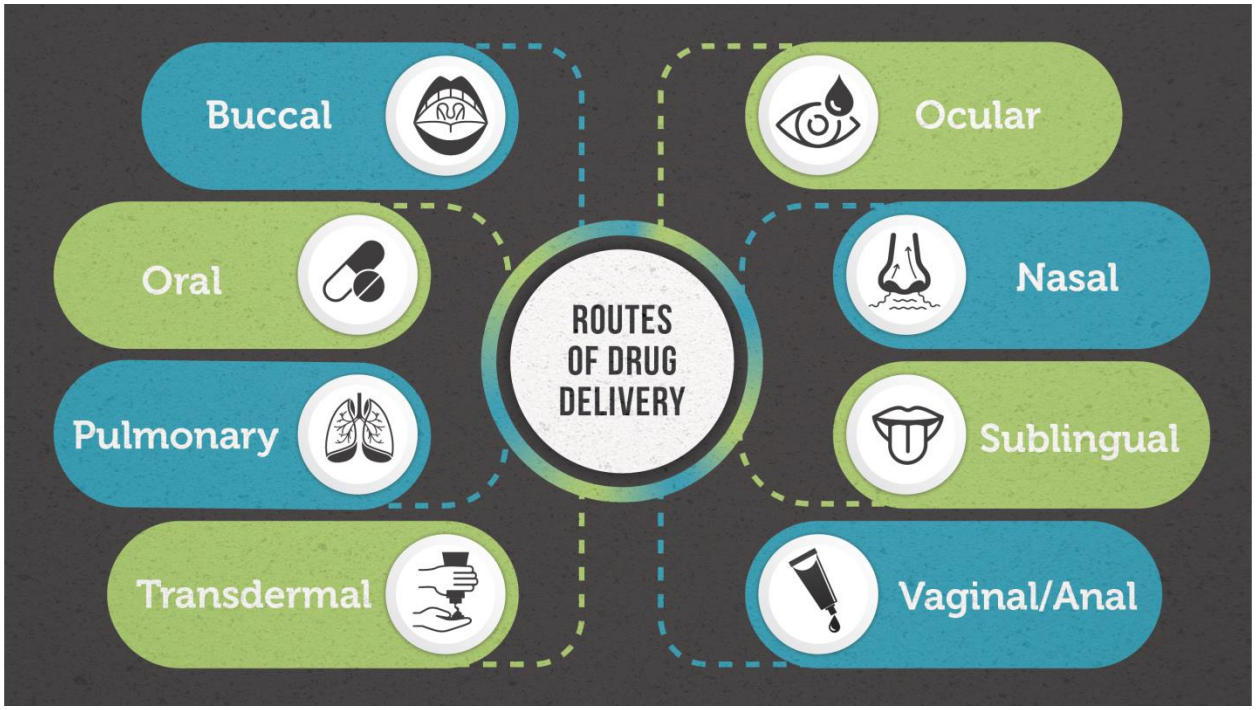


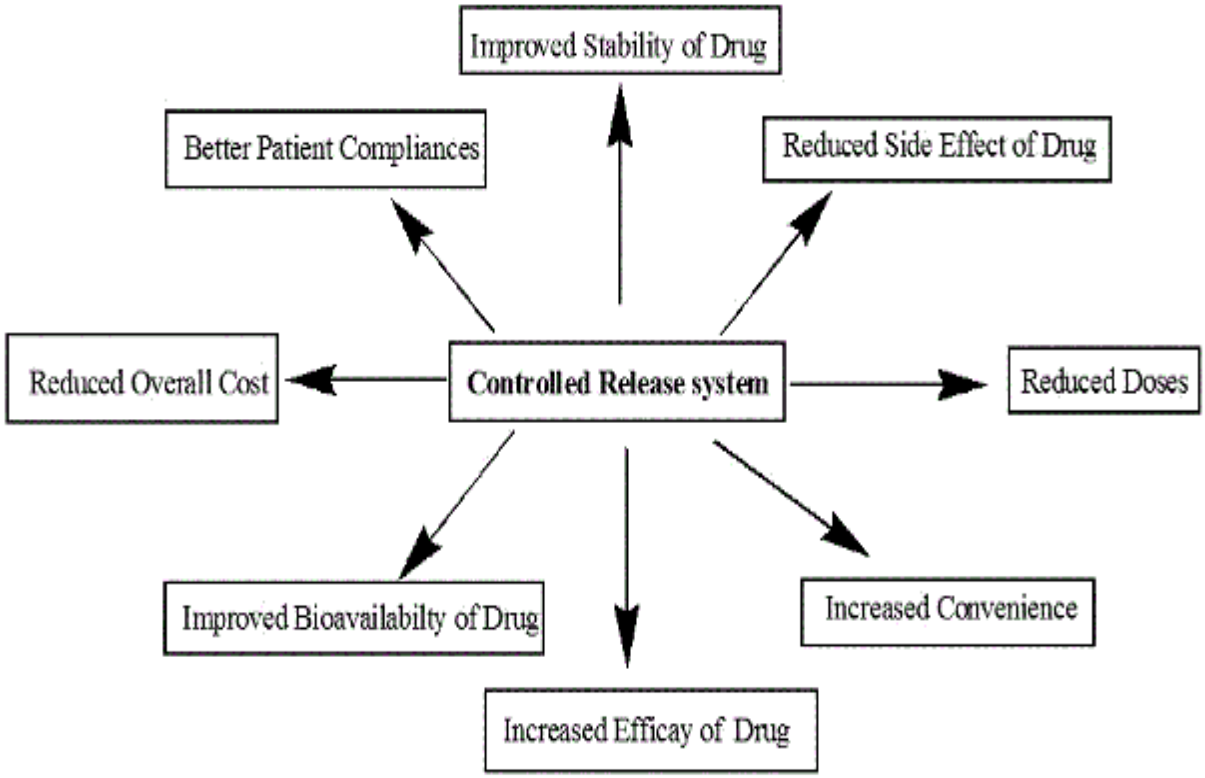
FIG 1.1: Drug delivery system

Drawback of conventional dosage form:

1) Poor patient compliance: Chances of missing of the dose of a drug.
2) The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of Drawback of conventional dosage form.

4) The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur. [6,7,8]

ADVANTAGES



1] Therapeutic advantage:
Reduction in drug plasma level fluctuation, maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

2] Reduction in adverse side effects and improvement in tolerability:
Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage form.

3] Patient comfort and compliance:
Oral drug delivery is the most common and convenient for patient and a reduction in dosing frequency enhances compliance.

4] Reduction in Health care cost:
The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increases as we approach the maximum safe concentration.
Avoid night time dosing: It also good for patients to avoid the at night time.

5] Economy: The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less.[9,10]

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM:

1] Dose dumping:
Dose dumping is a phenomenon whereby relatively large quantity of drug in a controlled release formulation is rapidly released, introducing potentially toxic quantity of the drug into systemic circulation. Dose dumping can lead to fatalities in case of potent drugs, which have a narrow therapeutic index.

2] Less flexibility in accurate dose adjustment:
In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two

fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

3] Poor In-vitro In-vivo correlation:

In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so- called 'absorption window' becomes important and may give rise to unsatisfactory drug absorption in-vivo despite excellent in-vitro release characteristics.

4] Increased potential for first pass clearance:

Hepatic clearance is a saturable process. After oral dosing, the drug reaches the liver via portal vein. The concentration of drug reaching the liver dictates the amount metabolized. Higher the drug concentration, greater is the amount required for saturating an enzyme surface in the liver. Conversely, smaller the concentration found with the controlled release and a sustained release dosage form, lesser is the possibility of saturating the enzyme surface. The possibility of reduced drug availability due to the first pass metabolism is therefore greater with controlled release and sustained released formulation than with conventional dosage form.

MATERIALS:

Propranolol-Procured From Torrent Pharmaceuticals Ltd, Gujarat, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad.,Eudragit S -100 Jaxani Pharma, (Ahmedabad), India,HPMC-K4 M Merck Specialities Pvt Ltd, Mumbai, India,HPMC-K15 M Merck Specialities Pvt Ltd, Mumbai, India,PVP K30-Loba Chemicals., Mumbai, India,Mg-Stearate-Merck Specialities Pvt Ltd, Mumbai, India,Talc-Merck Specialities Pvt Ltd, Mumbai, India,MCC-Merck Specialities Pvt Ltd, Mumbai, India

METHODOLOGY:

a) Determination of absorption maxima:

100mg of Propranolol pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

100mg of Propranolol pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5, 10, 15, 20 and 25 µg/ml of Propranolol per ml of solution. The absorbance of the above dilutions was measured at 289 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

7.2. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Formulation composition for tablets

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Propranolol	10	10	10	10	10	10	10	10	10	10	10	10
Eudragit S 100	10	20	30	40	-	-	-	-	-	-	-	-
HPMC K4 M	-	-	-	-	10	20	30	40	-	-	-	-
HPMC K15 M	-	-	-	-	-	-	-	-	10	20	30	40
PVP K30	8	8	8	8	8	8	8	8	8	8	8	8
Mg-Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4	4	4	4
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total Weight	150	150	150	150	150	150	150	150	150	150	150	150

All the quantities were in mg

RESULTS AND DISCUSSION:

Standard Calibration curve of Propranolol:

Table : Concentration and absorbance obtained for calibration curve of Propranolol in 0.1 N hydrochloric acid buffer (pH 1.2**)**

Conc [µg/mL]	Abs
0	0
5	0.158
10	0.291
15	0.432
20	0.554
25	0.681

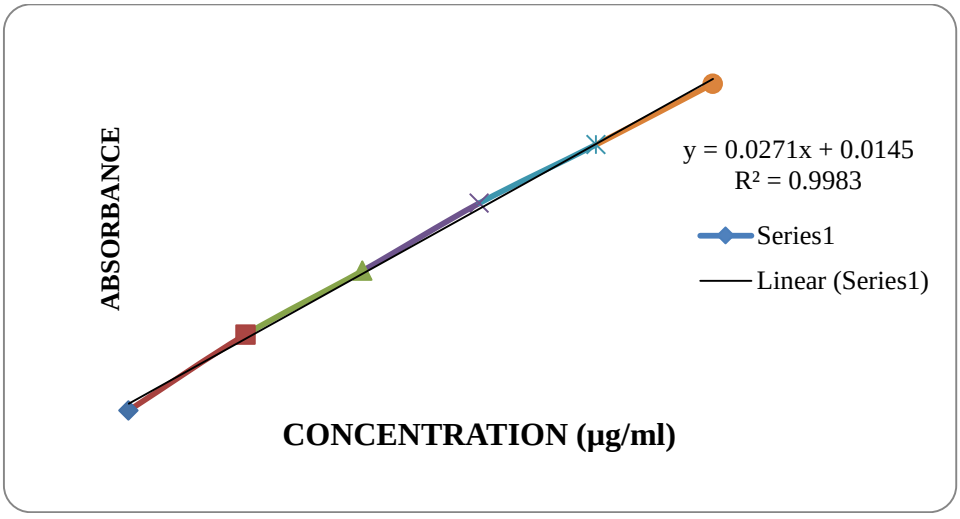


Fig 8.1 : Standard graph of Diltiazem HCl in 0.1 N HCl

Table 8.2: Concentration and absorbance obtained for calibration curve of Propranolol in pH 6.8 Phosphate buffer.

S. No.	Concentration(µg/ml)	Absorbance* (at 290 nm)
1	0	0
2	5	0.132
3	10	0.259
4	15	0.362
5	20	0.476
6	25	0.585

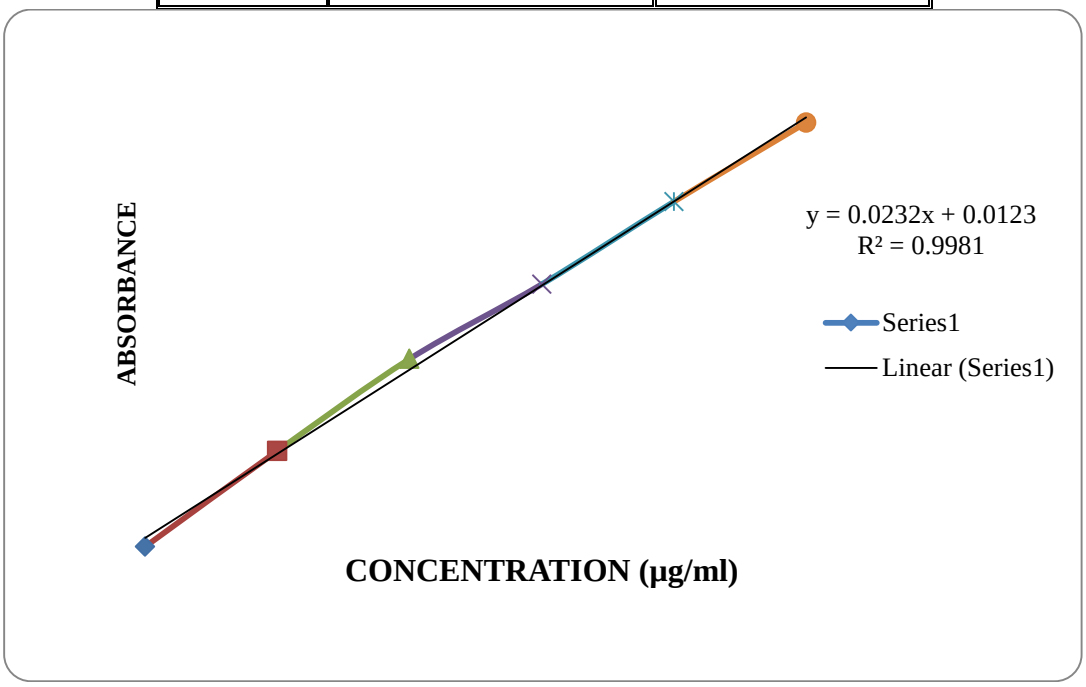


Fig 8.2: Standard graph of Propranolol in pH 6.8 Phosphate buffer

Preformulation parameters of powder blend

Table : Pre-formulation parameters of Core blend

Table 8.3: Pre-compression parameters					
Formulations	**Bulk Density(gm/cm²)**	**Tap Density (gm/cm²)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(Θ)**
F_1	0.307±0.07	0.310±0.05	14.7±0.06	1.17±0.05	23.7±0.11
F_2	0.304±0.09	0.341±0.09	11.4±0.05	1.14±0.07	23.4±0.08
F_3	0.301±0.09	0.371±0.11	15.1±0.09	1.11±0.05	24.1±0.16
F_4	0.312±0.12	0.321±0.08	10.8±0.06	1.18±0.09	24.8±0.12
F_5	0.305±0.14	0.350±0.09	12.5±0.13	1.15±0.06	24.5±0.09
F_6	0.308±0.08	0.381±0.08	13.2±0.08	1.12±0.09	25.2±0.11
F_7	0.313±0.09	0.331±0.13	11.3±0.11	1.19±0.07	24.9±0.12
F_8	0.306±0.12	0.363±0.09	11.6±0.05	1.16±0.05	23.6±0.09
F_9	0.319±0.15	0.390±0.11	13.9±0.05	1.13±0.07	24.3±0.13
F_{10}	0.308±0.17	0.354±0.16	13.2±0.05	1.12±0.07	25.2±0.13
F_{11}	0.315±0.13	0.322±0.04	11.4±0.07	1.14±0.08	23.4±0.07
F_{12}	0.309±0.11	0.377±0.07	13.8±0.10	1.18±0.11	22.8±0.06

8.2.2. Post compression Parameters:

Average weight test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 8.4. The average weight of the tablet is approximately in range of 146.78 to 150.1 mg, so the permissible limit is ±5% (150 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 4.1 to 4.9 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 2.15 to 2.95 mm.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 8.4. The average friability of all the formulations lies in the range of 0.17 to 0.72 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 95.28 -99.41%.

***In-Vitro* Dissolution studies:** *In-Vitro* dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours. The samples were withdrawn at regular time intervals of 30 min,1 hour,2 ,3,4,5,6,7,8,9, 10,11 and 12 hours respectively. The results were displayed in table 8.5.

Table 8.5: *In -vitro* dissolution data

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	27.52	22.60	23.32	43.53	17.75	13.61	13.62	8.25	31.3	8.16	11.08	21.91
2	34.11	35.82	46.67	46.39	24.98	24.18	16.17	11.71	54.0	14.36	14.31	24.56
3	41.75	41.91	51.23	51.48	31.57	27.27	21.34	24.59	57.1	22.84	23.64	37.15
4	52.24	44.76	54.47	64.32	42.92	32.69	34.23	27.31	62.5	35.33	26.72	39.28
5	55.96	53.95	57.62	67.67	55.11	45.41	42.60	32.29	65.1	43.94	31.09	42.87
6	68.21	66.72	59.83	70.52	58.35	58.61	45.57	35.40	73.2	51.41	42.15	55.19
7	86.79	75.95	60.76	72.28	63.42	63.83	53.82	48.01	86.4	54.66	55.16	58.69
8	99.63	85.10	62.91	75.32	66.57	66.71	61.71	53.32	92.5	62.07	57.85	63.38
9		91.86	68.54	83.94	72.20	72.82	65.22	56.75		75.14	69.41	66.79
10		94.25	69.43	85.71	75.39	75.29	79.99	62.21		83.37	74.03	73.33
11			73.27	88.15	81.48	80.32	81.18	65.98		96.05	75.81	76.94
12			78.56	89.40	87.21	93.53	98.29	74.25		97.92	83.32	79.68

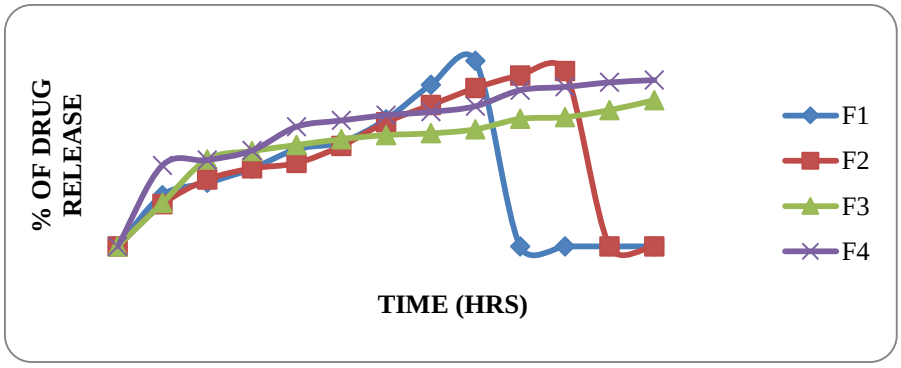


Fig 8.3: Dissolution profile of formulations prepared with Eudragit S 100 polymer

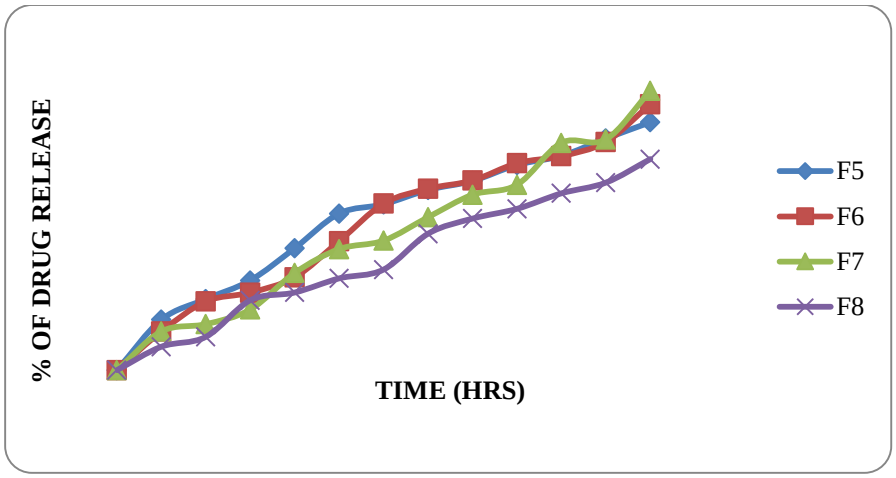


Fig 8.4: Dissolution profile of formulations prepared with HPMC K4 M polymer

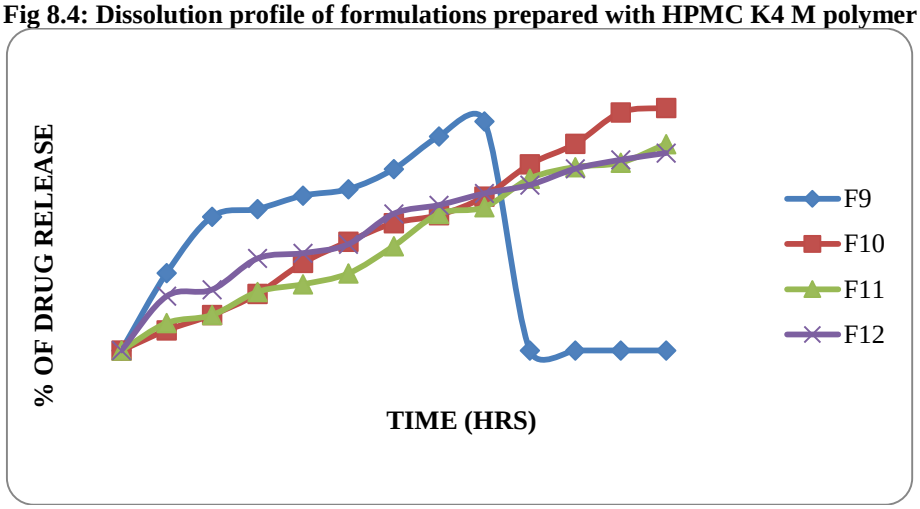


Fig 8.5: Dissolution profile of formulations prepared with HPMC K15 M as polymer

From the tabular column 8.5 it was evident that the formulations prepared with Eudragit S 100 as retarding polymer in low concentrations the polymer was unable to produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was also increased. Eudragit S 100 in the concentration of 40 mg showed good % drug release i.e., 89.40 in 12 hours.

Where as in case of formulations prepared with HPMC K4 M as retarding polymer, the formulations with 30 mg concentration of polymer showed complete drug release in 12 hours only, whereas the concentration of polymer increases the retarding nature also increased. The Formulation Containing HPMC K4 M in 30 Mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.29 %.

Where as in case of formulations prepared with HPMC K15 M as retarding polymer, the formulations with 10 mg concentration of polymer showed complete drug release in 12 hours only, The Formulation Containing HPMC K15 M in 20 Mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 97.92 %.
From the above results it was evident that the formulation F7 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data:
Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release mode

Table : Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
13.62	1	1.000	1.134	0.000	1.936	13.620	0.0734	-0.866	86.38	4.642	4.420	0.221
16.17	2	1.414	1.209	0.301	1.923	8.085	0.0618	-0.791	83.83	4.642	4.377	0.265
21.34	3	1.732	1.329	0.477	1.896	7.113	0.0469	-0.671	78.66	4.642	4.285	0.357
34.23	4	2.000	1.534	0.602	1.818	8.558	0.0292	-0.466	65.77	4.642	4.037	0.605
42.6	5	2.236	1.629	0.699	1.759	8.520	0.0235	-0.371	57.4	4.642	3.857	0.784
45.57	6	2.449	1.659	0.778	1.736	7.595	0.0219	-0.341	54.43	4.642	3.790	0.852
53.82	7	2.646	1.731	0.845	1.664	7.689	0.0186	-0.269	46.18	4.642	3.588	1.054
61.71	8	2.828	1.790	0.903	1.583	7.714	0.0162	-0.210	38.29	4.642	3.371	1.271
65.22	9	3.000	1.814	0.954	1.541	7.247	0.0153	-0.186	34.78	4.642	3.264	1.377
79.99	10	3.162	1.903	1.000	1.301	7.999	0.0125	-0.097	20.01	4.642	2.715	1.927
81.18	11	3.317	1.909	1.041	1.275	7.380	0.0123	-0.091	18.82	4.642	2.660	1.982
98.29	12	3.464	1.993	1.079	0.233	8.191	0.0102	-0.007	1.71	4.642	1.196	3.446

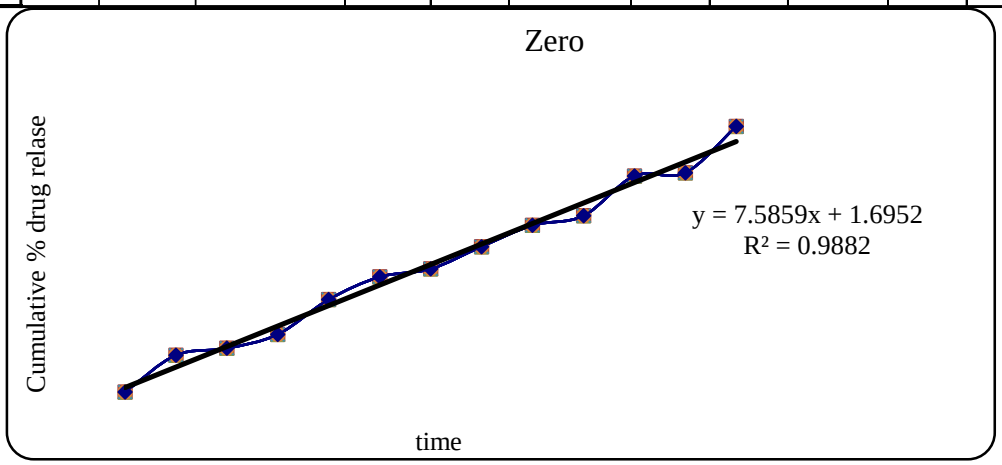


Fig 8.7 : Zero order release kinetics graph

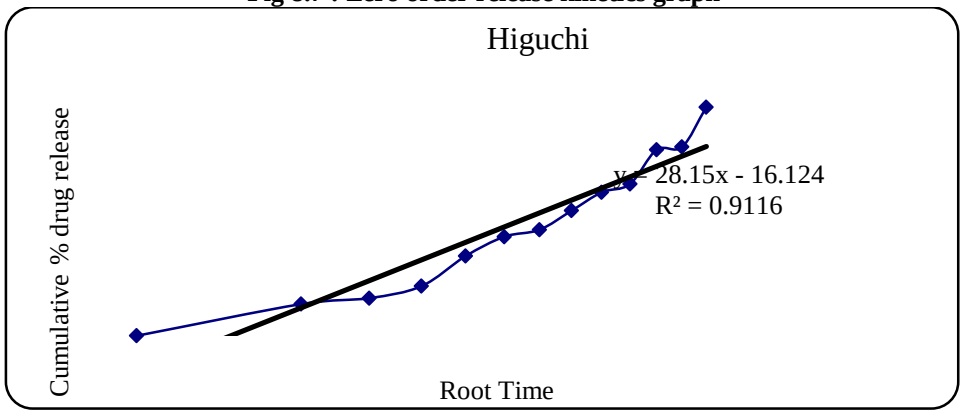


Fig 8.8 : Higuchi release kinetics graph

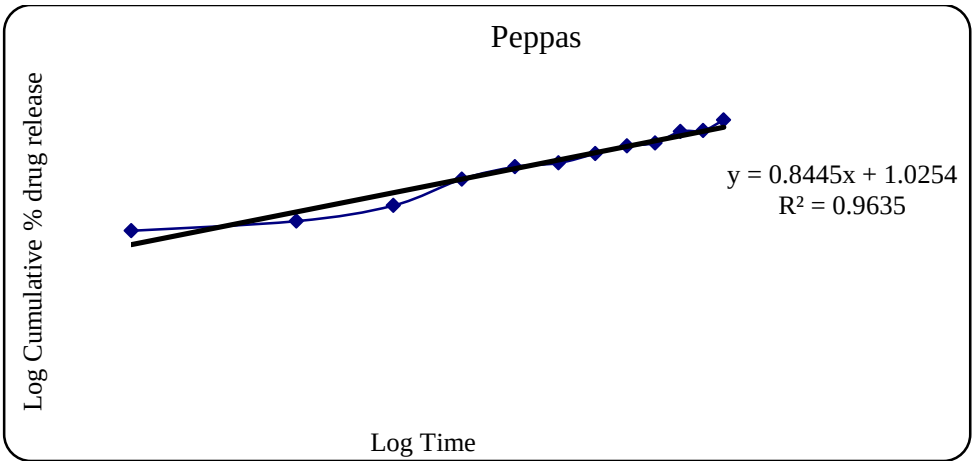


Fig 8.9: Kars mayer peppas graph

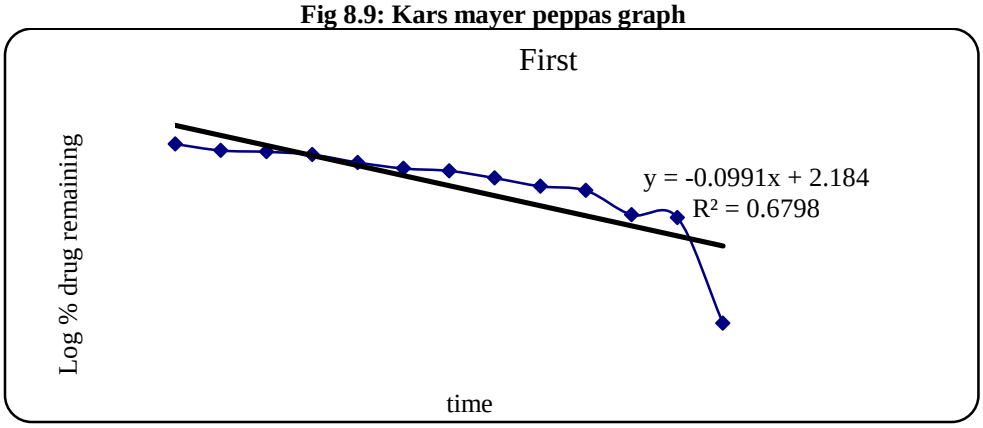


Fig 8.10: First order release kinetics graph

From the above graphs it was evident that the formulation F7 was followed Zero order release mechanism.

Fourier Transform-Infrared Spectroscopy:

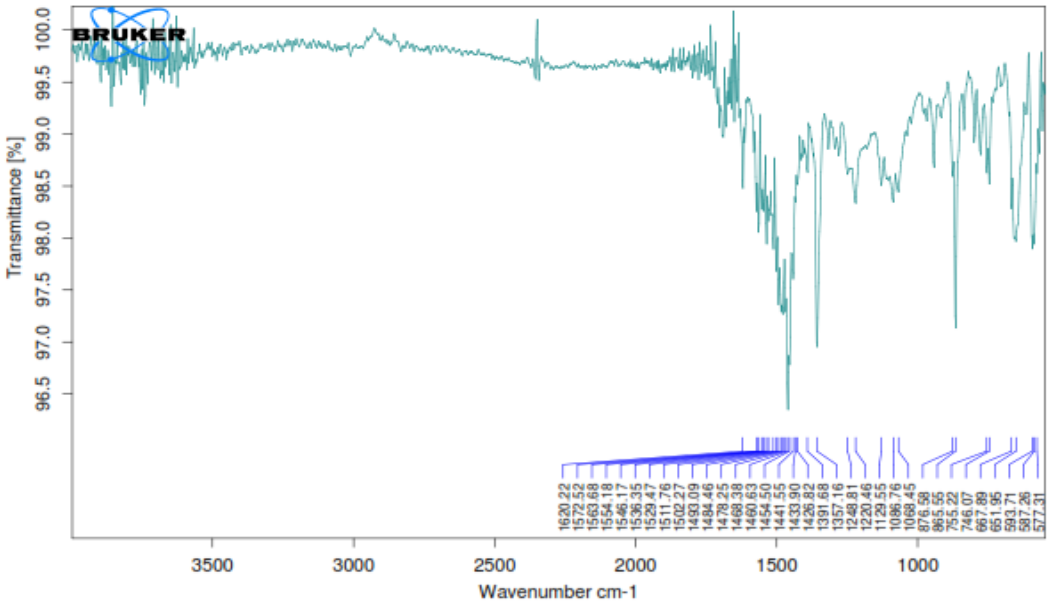


Fig no 8.3 :FT-TR Spectrum of Propranolol pure drug

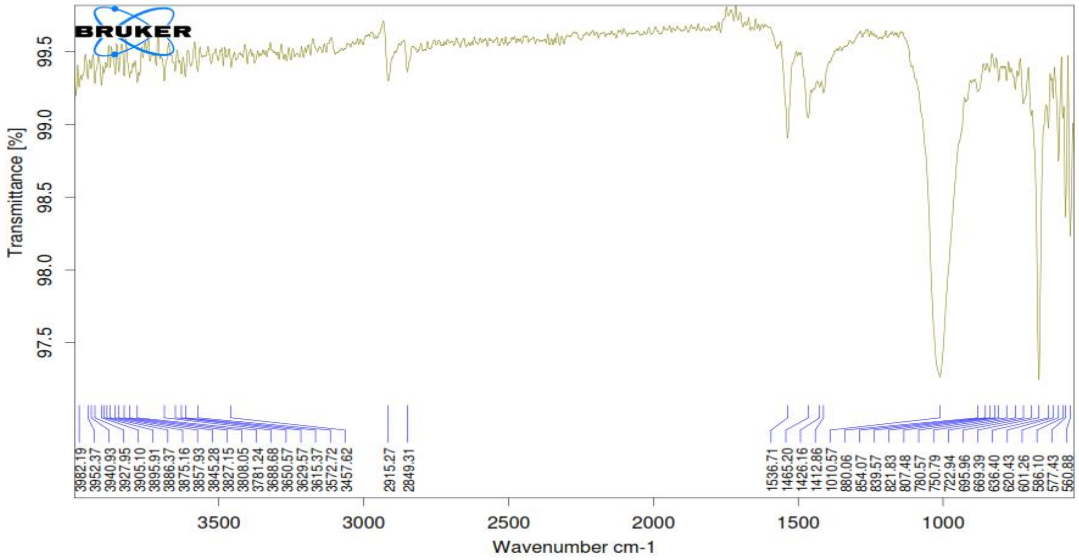


Fig No 8.4 :FT-IR Spectrum of Optimised Formulation

There is no incompatibility of pure drug and excipients. There is no disappearence of peaks of pure drug and in optimised formulation.

CONCLUSION:

Controlled release tablets Propranolol was formulated by direct compression method using the semi synthetic polymers Eudragit S 100, HPMC K4 M and HPMC K15 M. Infrared spectra of the drug along with polymers reveal that there is no significant interaction between drug and polymers. Preformulation studies were done initially and the results were found within the limits. The evaluation tests results are found to be within Pharmacopeial specifications. From *in-vitro* dissolution study it was concluded that the formulation F7 containing HPMC K4 M in the ratio 1:3 was taken optimized formulation of Controlled release tablet for 12 hours release as it fulfills all the requirement of Controlled release tablets. Kinetic studies were observed as Zero order release mechanism.

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