Design Sustained Release Bi-Layer Tablet of Antihypertensive Drug for Improved Drug Delivery

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Abstract--**The aim of present study is to design sustained release Bilayer tablet of Antihypertensive drug for improved drug delivery. To develop stable formulation of Antihypertensive drugs. To develop improved beneficial technology to overcome the shortcoming of the single tablet. To design modified release drug product for optimization of therapeutic regimen. To ensure safety and to improve efficacy of drug as well as patient compliance. To study the effect of concentration of polymer on drug release. Evaluation of precompression parameters such as angle of repose, bulk density, tapped density.**

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes1. The term sustained release, prolonged release, modified release, extended release, or depot formulation are used to identify drugs delivery systems that are designed to achieve or extended therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

Bilayer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bilayer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bilayer tablets is a very different aspect for antihypertensive, diabetic, antiinflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bilayer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. Generally, tablets manufacturing principles remain the same, there is much more to consider because making multilayer tablets involves multiple often incompatible products, additional equipment and many formulation and operation challenges.

I. INTRODUCTION

Sustained release drug delivery system:

Generally speaking, tablet production principles are the same, but there are many more factors to take into account because creating multilayer tablets requires numerous, frequently incompatible goods, extra equipment, and several formulation and operating issues. Any medication or dose form with a sustained release (SR) pattern prolongs the medication's therapeutic action.

Sustain release formulations aim to release the medication at a predefined rate for the intended duration.

A sustained release system where the dosage forms regulate the drug's rate of appearance in the body rather than the biological absorption process.

To achieve a therapeutic level quickly and sustained the level for a given period of time, the dosage forms generally consist of two dosage

(1) Loading dosage (Di) = it gives burst release
(2) Maintenance dose (Dm) = it maintains the drug
(3) Concentration in plasma gives sustained effect.

Totaldosage=W=Di+Dm (1)

W=Di+Kr0Td (2)

Where Kr0 is the zero order rate constant for drug release and Td is the total time desired for sustained release from one dose.

If Dm begins the release of drug at the time of dosing (t =0)

W=Di+Kr0Td–Kr0Tp (3)

Tp the time of peak plasma level

Correlation factor Kr0 Tp is the amount of drug provided during the period from t - 0 the time ofpeak drug level Tp.

The total dose of such a system is

W=Di+(KeCd/Kr)Vd (4)

Kr = Rate constant of first order drug release
If DM begins releasing drug at t = 0 a correlation factor is required the correct expression is
W = Di + (KCd/Cr)vd – Kr Tp (5)
(Figure No. 1) shows ideal plasma concentration curves for immediate release (IR), zero order release (ZODDS), So to maintain a constant drug level the rate of drug absorption should be equal to the rate of elimination3-4

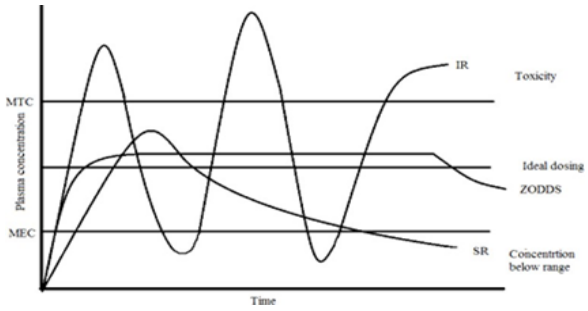

Fig no.1 Ideal plasma concentration curves for immediate release, zero order release andsustained release drug delivery system.

1. Drug Delivery System with Sustained Release
• Made to keep medication levels in the blood steady throughout time. • Replicates a continuous intravenous infusion (drug input equals drug elimination).

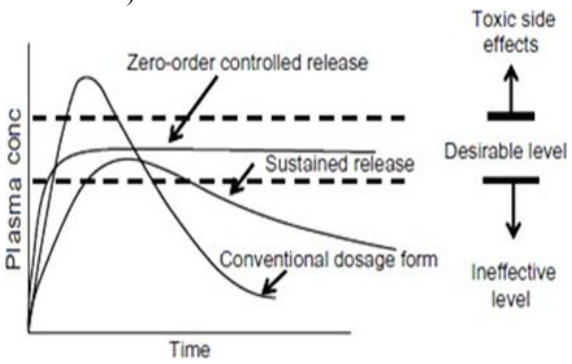

Fig no.2 Plasma drug concentration versus time for zero order controlled release,sustained release and release from conventional dosage forms

• Applications:
Loading dose (Di): quick initial impact
Maintenance dosage (Dm): keeps the medication level stable.
• The objective is to maintain a constant therapeutic focus and prevent oscillations.
Advantages
• Less frequent dosing
Improved adherence to treatment
• Consistent medication levels in the blood
• Less adverse effects
Disadvantages
• Increased price
• Challenging dose modification
• Drug action cannot be swiftly stopped • Unsuitable for medications with a limited window of absorption

2. Tablets (General) Benefits
• Precise dosage and affordable
• Simple to manufacture, handle, and transport • Excellent microbiological and chemical stability
Disadvantages
• Certain medications are difficult to compress. • A coating may be necessary if it is poorly soluble or tastes awful. • In certain situations, it might lower bioavailability

3. Tablets with Immediate Release (IR)
• Quick drug release and breakdown following administration
• Offer prompt action
Perfect Properties
• Quick dissolution
• Delicious flavor and mouthfeel • Stable and simple to produce
Advantages
• Quick action Elevated bioavailability
• Convenient and economical drawbacks
• Needs to be taken frequently
• Danger of elevated plasma concentration → poisoning

4. Tablets with Extended Release (ER)
• The medication is released gradually over extended periods of time (up to 24 hours). • Boost bioavailability and therapeutic efficacy

Important Drug Selection Factors
The solubility is moderate.
• Consistent in the GI system
• An appropriate molecular size
• Not strongly attached to proteins
• Throughout the GI tract, absorbed

Types of Extended release formulation
Many current oral extended-release systems are available
1. Dissolution-controlled release system.

2. Diffusion-controlled release system.
3. Osmotic pump system.
4. Erosion controlled release systems.

5. Tablets with two layers Bilayer Tablets
• Have two drug layers, such as immediate and sustained release. • Applied to controlled release or combination
therapy
Advantages
• Keep incompatible medications apart
• Regulate the rates of discharge
• Boost the efficacy of treatment

Bilayer tablet Challenges
• Separation of layers
• Variation in weight
• Complexity of manufacturing

6. High blood pressure, or Hypertension
• ≥140/90 mmHg is the definition. • Referred to be a "silent killer" since it frequently shows no symptoms
Types Hypertension
1. Crucial (most prevalent)
2. Secondary (caused by illness)
3. Malignant (extreme)
4. Pregnancy-related
5. Clinical anxiety, or white-coat

Complications in Hypertension
• Heart conditions
• A stroke
• Management of kidney damage
• Modifications to lifestyle:
Cut salt intake in half,Regular exercise, weight maintenance, and abstinence from smoking.

The aim of present study is to design sustained release Bi-layer tablet of Antihypertensivedrug for improved drug delivery.
To develop stable formulation of Antihypertensive drugs. Evaluation of pre-compression parameters such as angle of repose, bulk density, tappedDensity, Carr's index and Haunser's ratio.
Evaluation of post-compression parameters such as weight variation, thickness, hardness,friability, drug content, in-vitro drug release studies and in-vitro release kinetics studies.

II. MATERIAL AND METHODS

SrNo	Materials	Sources
1.	Propranolol	Concept pharma Aurangabad
2.	HPMC-15 m	Zim laboratories Ltd, Nagpur
3.	Microcrystalline cellulose	S.D fine chem limited, Mumbai
4.	Ethyl cellulose	Loba chemie Pvt. Ltd., Mumbai
5.	HPMC-100 C	S.D fine chem limited, Mumbai
6.	Sodium starch glycolate	Loba chemie Pvt. Ltd., Mumbai
7.	Polyvinyl-pyrrolidone	S.D fine chem limited, Mumbai
8.	Mg. stearate	Zim laboratories Ltd, Nagpur
9.	Talc	S.D fine chem limited, Mumbai

Various material were used to carry out the experimental work. The list of material used are given in the table no.
Table no.1 List if material used in formulation.

METHODS
A. Pre-formulation study
1. Organoleptic properties:
i.Color: A small quantity of propranolol HCL powders were taken in butter paper and viewed in well-illuminated place.
ii.Taste and odour: Very less quantity of propranolol HCL was used to get taste with the help of tongue as well as smelled to getthe odour.
2.Physical characteristics: Loss on Drying: Determined on 1.000 g by drying in an oven at 100°C to 105°C for 3 hours. Mix and accurately weigh the substance to be tested. The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2 - W3)}{(W2 - W1)} \times 100$$

Where, W1 = Weight of empty weighing bottle
W2 = Weight of weighing bottle + sample
W3 = Weight of weighing bottle + dried sample
1. Solubility Analysis:

1) Solubility: Solvents such as Methanol, alcohol and water and isopropyl alcohol are used for the solubility studies.

Descriptive Term	Parts of Solvent Required for 1 part ofSolute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble or Insoluble	Greater than or equal to 10,000

2)pH of the solution: Dissolved 6.50 gm of propranolol HCL in purified water and finally makes the volume up to 100 ml with purified water. Read the pH of that solution with the help of pH meter.

3)Melting point Melting points of propranolol HCL were determined, by taking the drug sample in small amount in a capillary tube closed at one end. Capillary tube containing drug was placed in melting point equipme The temperature at which the drug started melting and becomes liquid was noted

4)Partition coefficient The partition coefficient study of propranolol HCL was performed using noctanol as the organic phase and distilled water as the aqueous phase. drug concentration in aqueous phase and noctanol phases was determined spectrophotometrically Results are shown

5) Flow properties (Angle of Repose):
The angle of repose of granules was determined by funnel method.. The angle of repose was calculated by using equation:
Tan θ =h/r (or) θ = tan $^{-1}$(h/r)
Where, h and r are the height and radius of the powder cone.

Angle of repose (º)	Type of flow
<25	Excellent
25 – 30	Good
30 - 40	Poor
>40	Very poor

Table No: 2 Angle of repose as an indication of granule flow properties

a)Bulk density: (D_b)Procedure:
Weighed quantity of Propranolol HCL were transferred into a 50ml measuring
cylinder without tapping during transfer the volume occupied by granules was measured.
Bulk density (D_b) was measured by using formula.

$$D_b = m/V_o$$

Where, m: Mass of the blend
vo: Untapped Volume

b)Tapped density: (Dt) Procedure:
Weighed quantity of Propranolol was taken into a graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500/ 750 and 1250 taps in tapped density tester (Electro Lab USPII) According to USP , the blend was subjected for 500 taps the % Volume
variation was calculated by following formula

$$D_t = m/V_i$$

Where, m: Mass of the blendVi: Tapped Volume
c) Measurement of Powder Compressibility:

i. Compressibility Index:
The compressibility index of the granules was determined by the Carr's compressibility index

Carr's index (%)	Type of flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor

Table No: 3 Carr's index as an indication of granule flow properties Tapped density
ii. Determination of Hausner ratio:

It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

Flow character	Hausner's ratio
Excellent	1.00 – 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 –1.45
Very Poor	1.46 – 1.59
Very very Poor	> 1.60

Table No: 4 Hausner's ratio as an indication of granule flow properties

B. Analytical methods

1.Standard curve of propranolol HCL

1) Determination of absorption maxima (λ-max) of propranolol HCL

2) Preparation of standard plot of propranolol HCL in 0.1N HCL (pH1.2)

3) Preparation of standard plot in phosphate buffer (pH 6.8)

4) Preparation of standard plot in phosphate buffer (pH 7.4)

2.Dose calculation:- Half-life of propranolol HCL is 4 hrs.

3.Formulation of sustained release bilayer tablets

a. Preparation of blends for direct compression and wet granulation method

Composition of immediate release layer and sustained release layer are shown in Table no.5

Sr. No.	Ingredient	IR 1	IR 2	IR 3
1.	Propranolol	25	25	25
2.	S.S.G.	5	7.5	10
3.	Mannitol	60	57.5	55
4.	Aerosil	2.5	2.5	2.5
5.	PVP k30	5	5	5
6.	Mg. sterate	2.5	2.5	2.5
7.	Colorant	Q.S	Q.S	Q.S
	Total.	100	100	100

Table No: 5 Composition of propranolol HCL immediate release layer

Sr. no.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Propranolol HCL	55	55	55	55	55	55	55	55	55
2	Ethyl cellulose	27.5	55	82.5	-	-	-	-	-	-
3	HPMC k15	-	-	-	27.5	55	82.5	-	-	-
4	HPMC 100	-	-	-	-	-	-	27.5	55	82.5
5	MCC	162.5	135	107.5	162.5	135	107.5	162.5	135	107.5
6	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
	TOTAL	250mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg

Table: 6 Composition of propranolol HCL sustained release layer

1) Blends preparation of immediate release layer for direct compression method

The Propranolol layer was prepared by using direct compression method.

2) Blends preparation of sustained release layer for direct compression method

Drug and all the excipient except the magnesium stearate were accurately weighed and passed through #80mesh screen.

b. Pre-compression evaluation of blends

1. Bulk density and tapped density

10 gm of blend was taken in 100 ml measuring cylinder. Without troubling the cylinder the volume of powder was noted.

Bulk density (ρ) = Weight of sample /Bulk volume

Tapped density (ρb) =Weight of sample /Tapped

volume

2. Hausner quotient

Hausner ratio or quotient was calculated as the ratio of tapped to bulk densities.

Hausner′s quotient (ratio) =Tapped density /Bulk density.

3. Carr's index %

The Carr's index % of blends was calculated by using following formula.

Carrs index % = $\frac{Vtp-tp}{} \times 100$

Where, Vtρ= tapped density; Vρ= bulk density.

4. Angle of repose

The improper flow of powder is due to frictional forces between the particles. These friction forces were quantified by angle of repose.

c. Evaluation of sustained release bilayer tablets

1) Weight variation

The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

Sr. No.	Average weight of tablet (mg)	Maximum difference allowed
1.	130 or less	10
2.	130-324	7.5
3.	324<	5

Table No: 7 Weight variation Limit

2) Hardness test

The hardness of each batch of tablet was checked by using Monsanto hardness tester.

3)Friability

20 tablets were weighed and placed in the plastic chamber of Roches friabilator. The chamber was then rotated for four minutes at 25 rpm (a total of 100 revolutions). During each revolution tablets fall from a distance of 6 inches. After 100 revolutions the tablets were removed and weighed again.

4)Drug content

10 tablets were weighed from each batch and average weight is calculated. All tablets were crushed and powder equivalent to 55 mg drug was dissolved in phosphate buffer 7.4 and the volume was made up to 100 ml with pH 7.4 phosphate buffer. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH 7.4 phosphate buffers. Solution was filtered and absorbance was measured spectrophotometrically at 288 nm against pH 7.4 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

d. Dissolution studies

1) Drug Release Studies for Immediate release layer:- The in vitro dissolution of immediate release layer was determined using USP XXIII (basket method) dissolution apparatus.

2) Drug Release Studies for sustained release :- The in vitro dissolution of sustained release layer was determined using USP XXIII (basket method) dissolution apparatus.

3) Drug Release Studies for Bilayer Tablets:- The in vitro dissolution of Propranolol bilayer tablets were determined using USP XXIII (basket method) dissolution apparatus.

Dissolution test apparatus	USP type II
Speed	50 rpm
Stirrer	Paddle type
Volume of medium	900 ml
Volume withdrawn	5 ml
Medium used	7.4 phosphate buffer
Temperature	37±0.5ºC

Table No.8 Details data of dissolution test

e. Mathematical modelling of drug release profile:

1. Zero order kinetics: When the data is plotted as cumulative % drug release versus time, if the plot is linear then thedata obeys zero- order release Kinetics, with a slope equal to K0.

2. First order Kinetics: When the data is plotted as log cumulative % drug remaining versus time yields a straight line, indicating that the release follows first order kinetics.

3.Higuchi's model: When the data is plotted as cumulative drug release versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

4.Korsmeyer equation/ Peppa's model: When the data is plotted as log of drug released versus time, yields a straight line with a slope equalto „n" and the „K" can be obtained from y- intercept.

f. Stability studies:

The reason of stability testing is to provide evidence on how the quality of drug formulation varies with time under the influence of various environmental conditions such as temperature, humidity, light. From this study we know about recommended storage condition, re-test periods and shelf-life of the drug can be established. Stability studies are important for the following reasons.

1. This is an assurance given by the manufacturer that the patient would receive a uniform dose throughout the shelf life.
2. The drug control administration insists on manufacturers on conducting the stability studies, identity, strength, purity and quality of the drug for an extended period of time in the conditions of normal storage.
3. Stability testing prevents the possibility of marketing an unstable product. Both physical and chemical degradation of drug can result in unstable product. Purpose of stability studies: Stability studies are done to understand how to design a product and its packaging.

Storage conditions: Stability studies were carried out at 25ºC/60% and 40ºC/75% RH for a specific period of 3 months for the selected formulations.

III RESULT AND DISCUSSION

Pre-formulation studies

Characterization of propranolol HCL

1. Organoleptic Properties:

Test	Observations
Colour	White crystalline powder
Taste	Bitter salty
Odour	odourless

Table No.9 Organoleptic characterization of propranolol HCL

2. Physical characteristic:

a) Loss on Drying:

Test	Specification / limits	Observation
Loss on drying	Not more than 0.2 %	0.1%

Table No. 10 Loss on Drying

b) Angle of Repose

Sr.no.	Material	Angle of repose	Average angle Of repose
1.	Propranolol HCL	28º.37'	28^0. 56'
2.		29º.17'	
3.		28º14'	

Table No. 11 Angle of Repose of Bulk Drug

c) Determination Bulk density and Tapped density:

Sr.no.	Material	Bulk Density (gm / ml)	Average Bulk Density (gm / ml)	Tapped Density (gm / ml)	Average Tapped Density (gm /cc)
1	Propranolol HCL	0.364	0.359	0.531	0.533
2.		0.358		0.536	
3.		0.357		0.532	

Table No: 12 Determination of Bulk density and Tap density

Sr. No.	Drug	Partition coefficient (log P)
1.	Propranolol HCL	1.26±0.11

d) Powder Compressibility and Hausner's ratio

Materials	Compressibility index	Hausner ratio
Propranolol HCL	22.64	1.34

3. Solubility properties:

1) Solubility

Solubility study of drug (PRP) was performed in 0.1N HCL, distilled water; phosphate buffer pH 7.4 and results are presented in Table.

Sr. No.	Solvent	Propranolol hydrochloride
1.	O.1HCL pH 1.2	138.27±0.1 mg/ml
2.	Distilled water	58.32±0.4 mg/ml
3.	Buffer pH 7.4	145.80±0.2 mg/ml

2) ph. of the solution:

The ph of the soluction was found to be 3 with the help of ph meter it was Detected.

S. No.	Drug	Melting point
1.	Propranolol HCL	158-164^{0C}

3) Melting point

4. Partition Coefficient

The partition coefficient of the drug was calculated by using the formula:

Partition coefficient, (k) = Amount of drug in organic layer / Amount of drug in aqueous layer

Partition coefficient is the measurement of drug's lipophilicity and its capability to cross cell membranes. It is defined as the fraction of unionized drug distributed between the organic and aqueous part at equilibrium.

Sr. No.	Drug	Partition coefficient (log P)
1.	Propranolol HCL	1.26±0.11

5. Analytical methods:

a. Standard curve of propranolol HCL (λ max)

1) Calibration curve of propranolol hydrochloride using HCL(pH1.2)

The calibration curve of propranolol HCL was prepared using 0.1N HCL pH 1.2, pophate buffer, pH 6.8 and 7.4, by using Ultravioletvisible (UV) spectroscopy.

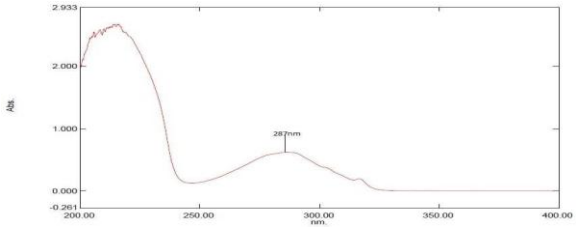

Figure No: 3 UV curve of propranolol HCL using 0.1N HCL (pH 1.2)

Sr. No.	Concentration µg/ml	Absorbance
1.	0	0
2.	10	0.237
3.	20	0.429
4.	30	0.639
5.	40	0.860
6.	50	1.073

Table No: 13 Calibration curve of propranolol HCL using 0.1N HCL (pH 1.2)

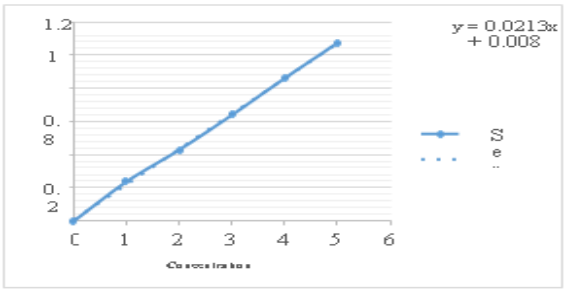

Figure No: 4 Standard curve of propranolol HCL using 0.1N HCL (pH 1.2)

1. Calibration curve of propranolol hydrochloride using HCL (pH 1.2)

The absorbance was determined at 288 nm for different concentrations in the range of 10, 20, 30, 40, 50µg/ml.

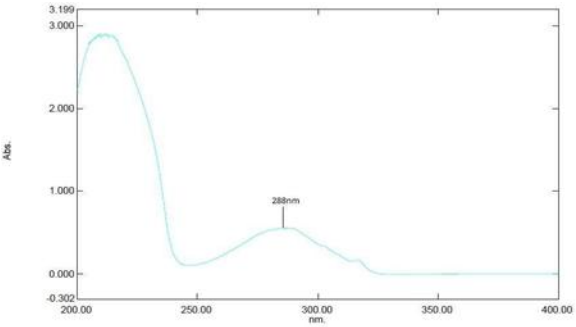

Figure No: 5 UV curve of propranolol HCL using phosphate buffer (pH 6.8)

Sr. No.	Concentration µg/ml	Absorbance
1.	0	0
2.	10	0.240
3.	20	0.395
4.	30	0.598
5.	40	0.794
6.	50	0.977

Table No: 14 Calibration curve of propranolol HCL using phosphate buffer (pH 6.8)

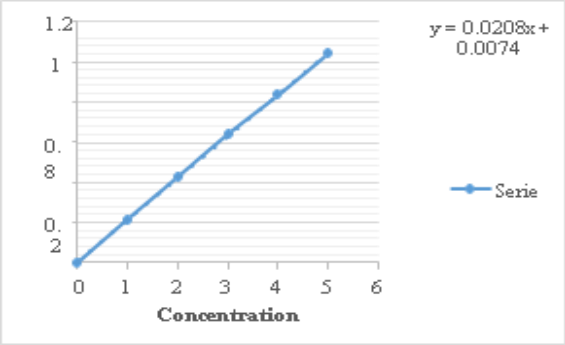

Figure No: 8 Standard curve of propranolol HCL using phosphate buffer (pH 7.4)

6. Fourier Transform infrared spectroscopy:

1) FTIR of propranolol HCL

The Infrared spectroscopy studies were conducted for pure drug (PRP). The main peaks of propranolol HCL, C16H21NO2 HCL, were at 3274 cm−1, 2803 cm−1, 1265 cm−1, and 823 cm- 1 represented secondary hydroxyl group, secondary amine group, aryl alkyl ether, and substituted naphthalene, respectively. The FTIR spectra of propranolol HCL.

FTIR range of peak(cm-1)	Presence of functional groupsin PRP
3274.30	Secondary Hydroxyl group
2803.02-2706.16	Secondary Amine
2494.38-2362.55	C=C stretching
1686.31 Sharp	Sharp N-H bending
1449.58	C-C Stretching
1265.32-1237.56 Sharp	Aryl alkyl ether
1168.29-1102.39 Sharp	Alkyl halide
957.65	=C-H Bend
899.25-823.97 Sharp	C-H of Aromatic
796.11-766.16 Sharp A	Substituted naphthalene

Table No: 16 FTIR interpretation of propranolol HCL

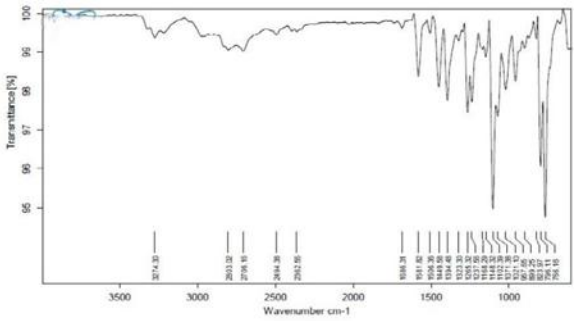

Figure No: 9 FTIR spectra of propranolol HCL

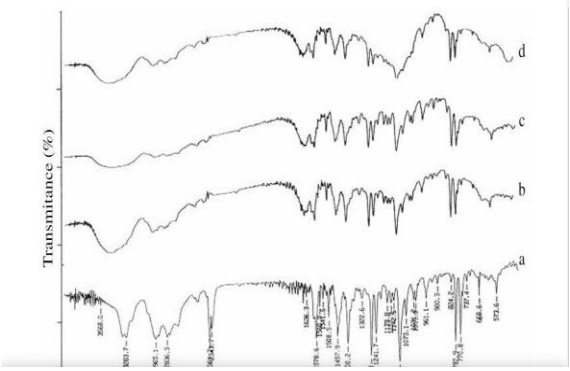

Figure No.10 FTIR spectra of propranolol (a), propranolol with ethyl cellulose (b),propranolol with HPMC K15(c), Propranolol with HPMC K100 (d).

rom the results, it was concluded that there was no interference of the functional group as the principle peaks of the PRP were found to be unaltered in the drugpolymer physical mixtures, indicating that they were compatible chemically. The spectrum confirmed that there is no significant change in the chemical integrity of the drug.

7. Prepared Bi-layer sustained release Anti-hypertensive Tablet:

Fig No.11 Prepared Bi-layer sustained release Anti-hypertensive Tablets

8. Evaluation Parameters:

a) Evaluation of powder blended characteristics of Bilayer tablet formulation ofPropranolol

Bulk density was found in the range of 0.2785±1.2 0.3240±1.4 for immediate release & 0.2237 0.3642 g/cm3 for sustained release. And the tapped density between0.3756±0.0014 0.4500±0.0012 for IR & 0.3810 0.4880g/cm3 for sustained release indicating both parameters were found to be within the limits. Using the above two density data, Carr's compressibility index were calculated. The compressibility index and Hausner's ratio was found in the range of 9.21 12.54 fir IR & 7.2718.42 % and 1.0531.24 for sustained release respectively indicating that all powder blends showed excellent to acceptable flow properties. The flow property of all powder blends was better explained from angle of repose. The angle of repose was found in the range of 25.25±0.23 27.14±0.14 fir IR & 25.3331.43° for sustained release. The results of angle of repose showed all powder blends exhibited good to acceptable flow property. The results of precompression parameters are shown in table no: 17

Formulations Number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner'sRatio	Angle of Repose (θ)
IR 1	0.2785±1.2	0.4500±0.0012	10.21±0.325	1.035±0.0025	26.85±0.14
IR 2	0.2883±1.8	0.3756±0.0014	9.21±0.0456	1.231±0.0014	27.14±0.68
IR 3	0.3240±1.4	0.3932±0.00021	12.54±147	1.0512±0.0056	25.25±0.23
F1	0.2237±1.1	0.3810±0.0045	7.27±0.659	1.177±0.0076	29.73±0.41
F2	0.3642±1.8	0.4120±0.0026	7.58±0.514	1.053±0.0060	25.33± 0.63
F3	0.2836±1.0	0.4120±0.005	7.43±0.760	1.059±0.0088	28.44± 0.35
F4	0.2090±1.6	0.4270±0.0037	13.78±0.386	1.073±0.0053	27.48±0.52
F5	0.3457±0.8	0.4600±0.0024	17.31±0.794	1.224±0.011	31.34± 0.13
F6	0.2882±1.9	0.4880±0.0065	18.42±0.120	1.24±0.0020	28.26±0.43
F7	0.2240±0.3	0.3923±0.0023	8.56±0.230	1.054±0.0023	26.54±0.12
F8	0.2536±1.5	0.4498±0.0048	11.65±0.198	1.211±0.0012	30.47±0.54
F9	0.3285±1.2	0.4025±0.0014	14.21±0.114	1.056±0.0077	26.11±0.14

Table No.17 Evaluation parameters of pre-formulation characteristics of powder blend

2. Post-compression parameters

Formulation	Diameter (mm)± SD	Thickness (mm)± SD	Weight variation(mg)	Hardness (kg/cm2)	riability(%)	integrationtime	Drug content (%)
IR 1	4.25±0.014	1.2±0.065	99.45±0.17	3.7±0.06	0.12±0.07	30±0.10	98.25±0.02
IR 2	3.95±0.016	1.6±0.041	99.25±0.14	3.8±0.32	0.14±0.10	25±0.14	97.65±0.14
IR 3	5.41±0.19	2.1±0.014	100.12±0.014	3.7±0.74	0.19±0.14	15±0.65	99.25±0.19

Table No: 18 Post-compression parameter for immediate release tablet

From the above observation it was found that IR 3 shows good result. So it will be used asoptimized batch

Formulation	Diameter(mm)± SD	Thickness (mm)± SD	Weight variation(mg)	Hardness (kg/cm2)	Friability(%)	Drug content (%)
F1	7.82±0.012	3.9±0.09	250.89±0.12	7.3±0.04	0.64±0.007	97.75±0.025
F2	7.80±0.002	4.0±0.02	253.88±0.60	7.8±0.03	0.52±0.005	98.25±0.044
F3	7.85±0.007	4.2±0.01	251.12±0.52	8.0±0.07	0.58±0.031	98.31±0.037
F4	7.84±0.022	3.9±0.07	249.81±0.13	6.5±0.04	0.72±0.016	96.23±0.025

F5	8.0±0.015	4.0±0.04	250.80±0.32	6.8±0.08	0.42±0.09	98.37±0.058
F6	7.94±0.010	3.8±0.09	248.92±0.44	7.1±0.03	0.42±0.01	99.12±0.23
F7	7.88±0.021	3.8±0.01	247.69±0.55	6.6±0.01	0.40±0.002	97.61±0.08
F8	8.0±0.014	4.0±0.09	250.01±014	7.2±0.02	0.56±0.025	98.56±0.22
F9	7.89±0.047	4.1±0.01	252.12±0.01	7.1±0.01	0.71±0.012	99.67±0.07

Table No: 19 standard physical tests for Bilayer tablets

Discussion about the physical parameters such as

A. Thickness of tablets
B. Hardness
C. Friability
D. Weight Variation
E. Drug content

A. Tablet thickness:

The average thickness for each formulation was found to be between 3.8 and 4.2 mm, which is within the permitted limit of deviation, or 5% of the standard value. Additionally, all pill formulations had crown diameters between 8.0 and 7.8 mm

B. Hardness:-

The hardness test was carried out using a "Monsanto hardness tester." The average hardness of each formulation ranges from 6.0 to 8.0 kg/cm2.

C.Friability The average percentage friability for all formulations was determined to be between 0.40% and 0.72%, which isdiscovered to be less than 1%, or inside the pharmacopoeial limit.Thus, F4 had the highest friability of 0.72%, while F7 had the lowest friability of 0.40.7%.

D. Test for weight variation:

The weight variation for all formulations, which was found to be between 249.92 and 253.88 mg.Since the weight variation percentage was within the pharmacopoeial limitations (<5%), all of the prepared tablets passed the weight variation test. It was discovered that all of the tablets had consistent weights with minimal standard deviation values.

E. Content of Drugs

The medication content % for formulations F1 through F9 was found to be between 96.23%w/wand 99.67%w/w. It complies with official specifications.

9. In-vitro Drug release studies:

All of the immediate release layer batches demonstrated drug release within 20 to 30 minutes, according to the findings of in-vitro dissolution tests. However, the formulation IR3 was deemed the best batch to be included in the bilayer tablet formulation since it demonstrated the highest quantity of drug release, 99.10±0.95%, within 15 minutes in an immediate release manner.According to the findings of invitro drug release tests, the release rate of propranolol rose when the concentration of S.S.G. climbed from 5% to 10%.This is due to the reason that increased concentration of disintegrant lead to decreased disintegration time and thus increased release of Propranolol.

SR. No	Time (min)	IR-1	IR-2	IR-3
	0	0	0	0
1.	5	25.32±0.4	39.40±0.10	49.40±0.20
2.	10	40.50±0.10	50.13±1.4	75.30±0.21
3.	15	62.90±0.12	71.23±0.41	99.10±0.95
4.	20	78.90±0.21	84.54±0.10	
5.	25	89.40±0.40	97.90±10	
6.	30	98.10±0.11		

Table No.20 In-vitro disintegration data for IR-1, IR-2, and IR-3 Formulation

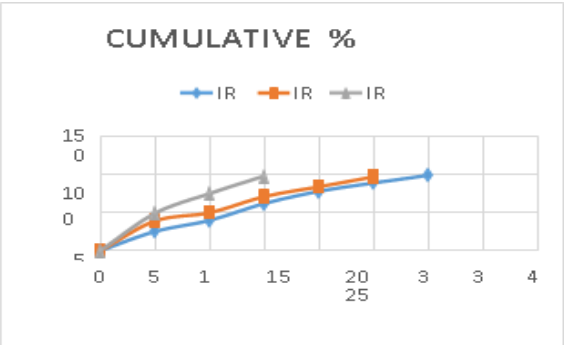

Figure No: 12 In-vitro disintegration data for IR-1, IR-2, and IR-3 Formulation

Time(hrs.)	Cumulative percent drug release		
	F7	F8	F9
0	0	0	0
1	22.94±0.08	19.12±0.3	18.14±0.8
2	29.91±0.11	25.87±0.15	23.25±0.7
3	50.13±0.12	38.56±0.10	31.12±0.3
4	55.6±0.42	47.41±0.6	38.62±0.95
5	62.4±0.13	56.96±0.15	46.93±0.17
6	70.13±0.12	68.92±0.14	57.81±0.9
7	78.95±0.14	75.53±0.12	65.10±0.11
8	82.61±0.66	86.66±0.94	72.5±0.6
9	97.26±0.13	95.98±0.1	81.62±0.7
10	97.41±0.78	97.49±0.18	91.17±0.18
11		98.82±0.33	95.62±0.8
12			97.62±0.94
13			98.03±0.17
14			99.67±0.1

Table No: 21 In-vitro dissolution data of F7, F8 and F9 Formulation

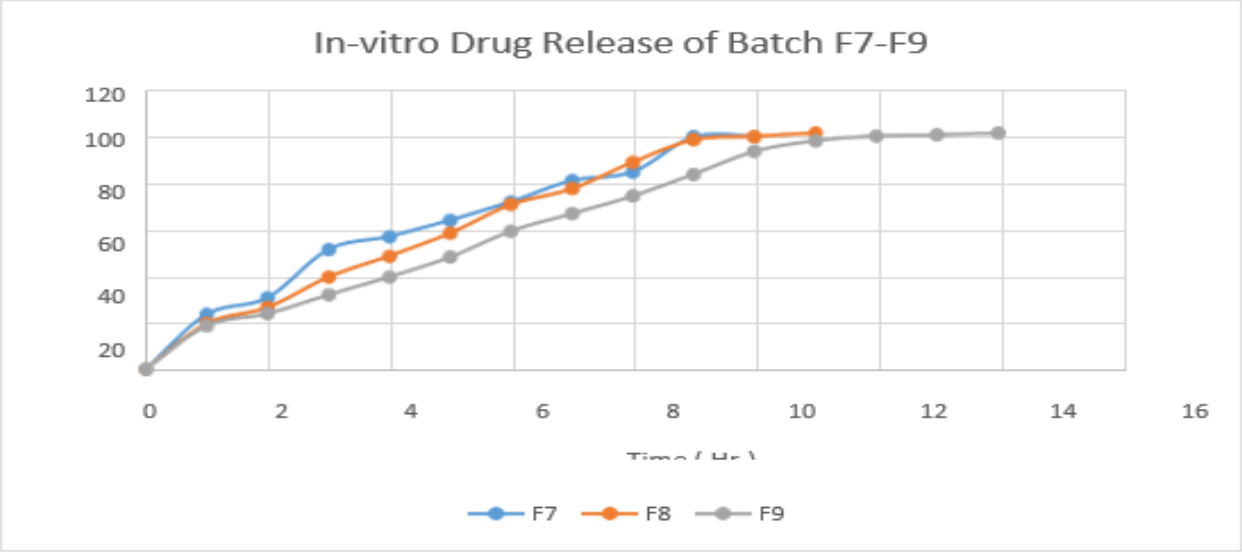

Figure 13 : F7, F8, and F9 formulations' in vitro dissolution profiles

The cumulative percent drug released vs. time was plotted to examine the release of propranolol hydrochloride from the produced formulations. A basic visual examination of the plot reveals an initial burst effect. During the first fifteen minutes of the dissolution testing, more than thirty percent of the propranolol hydrochloride from all the formulations was released. The formulation's immediate release layer is responsible for the initial high level of propranolol hydrochloride release.For twelve hours, further propranolol. Because the hydrophobic ethylcellulose on the tablet's surface prevents solvent

molecules from penetrating the system, EC decreases drug release; in other words, the permeability of the bilayer structure controls the rate of release. Propranolol hydrochloride release slows down as ethylcellulose content rises (Fig. 8.12).Figure demonstrates that the EC 1:0.5 formulation was unable to maintain the release for more than seven hours.Over the course of the 12hour test, formulations EC 1:1 and EC 1:1.5 demonstrated the intended release profile. In light of the minimal quantity of ethylcellulose needed to maintain the release for a duration of 12 hours, formulation EC 1:1 was chosen as the optimal formulation..

Table No: 22 Drug release kinetic studies of Optimized Batch F9 for sustained release bilayer tablets

In light of the minimal quantity of ethylcellulose needed to maintain the release for a duration of 12 hours, formulation EC 1:1 was chosen as the optimal formulation.

Similarly, HPMC K15 M (HPMC K15 M 1:0.5 and HPMC K15 1:1) and HPMC 100 (HPMC 100 1:0.5 and HPMC 100 1:1) formulations failed to maintain drug release for the intended 12hour durationHPMC K15 M 1:1.5 and HPMC 100 1:1.5, on the other hand, could maintain the release for 12 hours.As a result, Batch F9 was chosen as an optimal formulation. For the final two, the computed regression coefficients for the Higuchi, zero order, and first order models were 0.98462409, 0.9582674, and 0.882118879, respectively. Thus, the release appears to be appropriate for the Higuchi model.

10. Release Kinetics:

Regression coefficients were computed by fitting the invitro drug release data for PRP sustained release bilayer tablet formulations made using the direct compression approach to various kinetic models. Table No. displays the regression values and rate constants for the PRP sustained release bilayer matrix tablet formulations made by direct compression. The improved batch F9's release kinetics are listed below.

	Zero Order	First Order	Hixon Crowell	korse meyer peppasmodel	HiguchiPlot
R2 Value	0.9582674	0.75191007	0.882118879	0.334086587	0.98462409
Slope	0.119830952	0.00146414	0.009370415	0.727849504	0.24081498
Intercept	16.147	1.06591408	3.738612833	-1.965184889	2.88978641

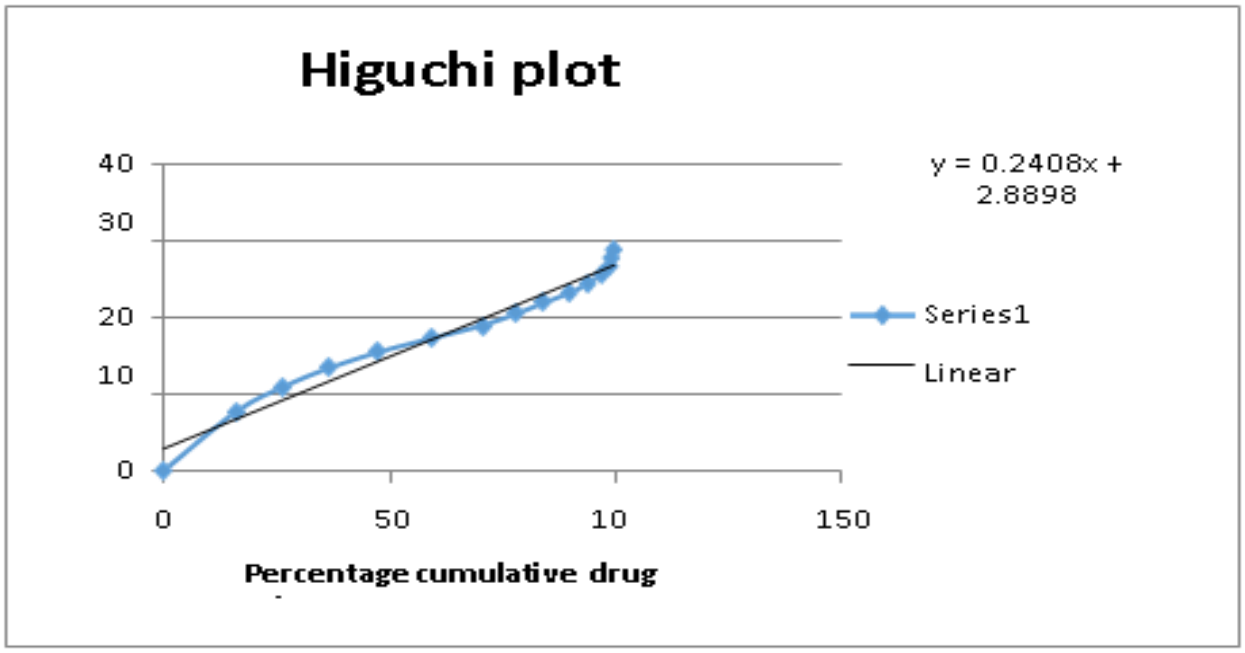

Fig no 14 Drug release kinetic studies of Optimized Batch F-9

11. Stability studies:

The two best formulations, F6 and F9, were chosen for stability tests at 25ºC/60% RH and 45ºC/75% RH based on the outcomes of in-vitro drug release. The stability studies were carried out using the procedure outlined in section four. The physical characteristics, hardness, friability, drug content, and in vitro drug release of the chosen formulations were assessed.

Storage period	Stored at 25ºC/60% RH			Stored at 45ºC/75% RH		
	Formulation F9			Formulation F9		
	Hardness Kg/cm2	% friability	% Drugcontent	HardnessKg/cm2	% friability	% Drugcontent
Initial	7.1±0.06	0.71±0.2	99.67±0.5	7.1±0.06	0.71±0.2	99.67±0.5
After 15days	6.5±0.16	0.57±0.3	99.6±0.1	6.4±0.11	0.55±0.1	97.5±0.3
After 30days	6.3±0.21	0.60±0.4	99.4±0.2	6.2±0.21	0.59±0.1	97.2±0.3
After 45days	6.2±0.15	0.62±0.3	98.3±0.6	6.0±0.23	0.61±0.3	97.0±0.3

Table No: 23 Results of stability studies for formulation F9 stored at 25ºC/60% and45ºC/75%RH

The physical appearance, hardness, friability, drug content, and drug release profile did not significantly alter over the course of the trial, according to the data. Stability tests conducted over a three-month period showed no discernible medication deterioration. As a result, the produced formulations were stable both chemically and physically.

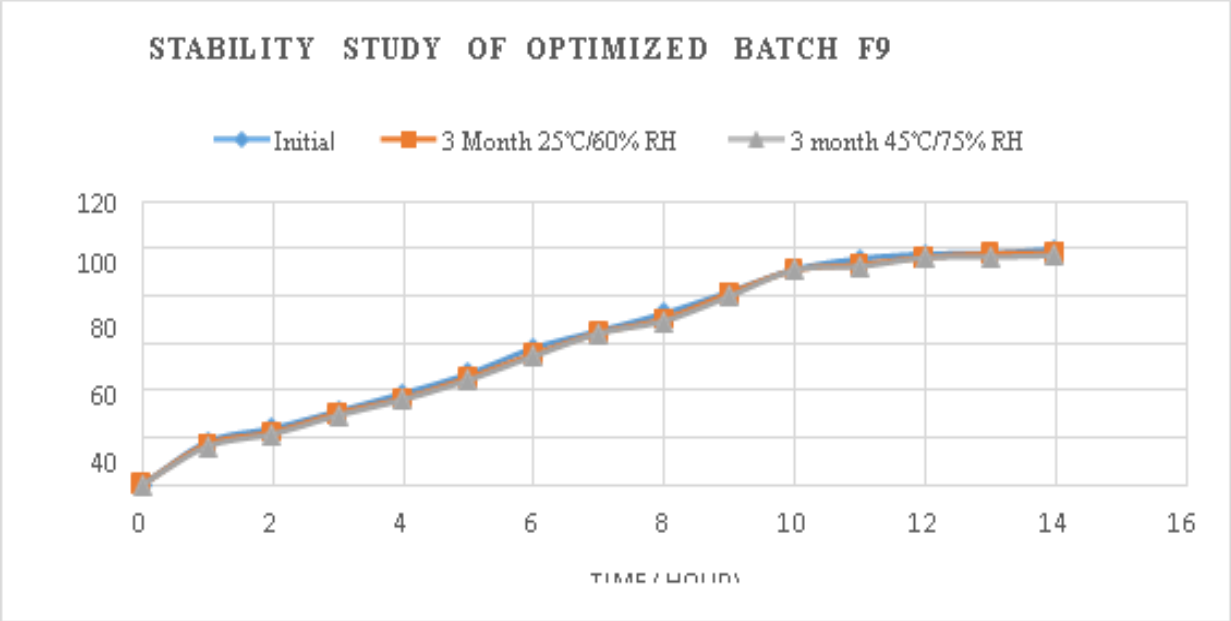

Fig No: 15 Results of stability studies for formulation F9 stored at 25ºC/60% and 45ºC/75%RH

IV. CONCLUSION

As a beta blocker, propranolol reduces blood pressure by blocking the activity of norepinephrine (noradrenaline) and epinephrine (adrenaline) at both β1- and β2-adrenergic receptors. The current study's goal was to find out if propranolol release from bilayer tablets made with various polymer concentrations could be sustained. After the powder mixes were crushed into tablets, postcompression parameters such as weight fluctuation, thickness,

hardness, friability, and drug content were assessed. Every formulation batch produced results that were satisfactory. The outcome can lead to the following conclusions. All formulations' preformulation examinations, including angle of repose, bulk density, tapped density, Haunses ratio, and Carr's index, were found to be with in determined to be within the typical bounds. FTIR analyses showed that the medication and other excipients did not interact chemically. After the powder mixes were crushed into tablets, postcompression parameters such as
weight fluctuation, thickness, hardness, friability, and drug content were assessed. Every formulation batch produced results that were satisfactory.

For a duration of 24 hours, the invitro drug release was investigated using USP Type II
dissolution apparatus in both intestinal fluid and simulated stomach fluid. The drug release was sustained over a 24hour period by formulations with higher concentrations of HPMC K15 M, or F6 (99.12%), and HPMC K 100, or F9 (99.67%). The drug release in vitro is first order, suggesting that the mechanism of drug release may
be non-Fickian.
According to stability studies, the tablet formulations remained stable for the duration of the stability period.It was determined that the polymer is a key component in the formulation of propranolol sustain release bilayer tablets.Ultimately, the study found that when the bilayer tablet had a larger concentration of polymers, the drug release was reduced.

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