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 Bi-layer tablet ofAntihypertensive 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 pre-compression parameters such as angle of repose, bulk density, tappe**

Index Terms—tablet, tablets Bilayer, Oral Extended release

I. INTRODUCTION

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 routes. 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. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer 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 bi- layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few.

Objective of sustained release drug delivery system

The objective of sustained release system is to deliver drug at a rate required to achieve and maintain constant level of drug in the blood. The rate should be similar to continuous Intravenous

(IV) infusion where a drug is provided to the patient at a constant rate just equal to its rate of elimination. This means that the rate of drug delivery must be independent of the amount of drug remaining in the dosage form and at constant over time.

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

Loading dosage (Di) = it gives burst release

Maintenance dose (Dm) = it maintains the drug

Concentration in plasma gives sustained effect.

Total dosage = $W=Di+Dm$ (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)

$W = Di + Kr0\ Td – Kr0\ Tp$ (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 of peak drug level Tp.

The total dose of such a system is

$W = Di + (Ke\ Cd/\ Kr)Vd$ (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. 1.1) 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

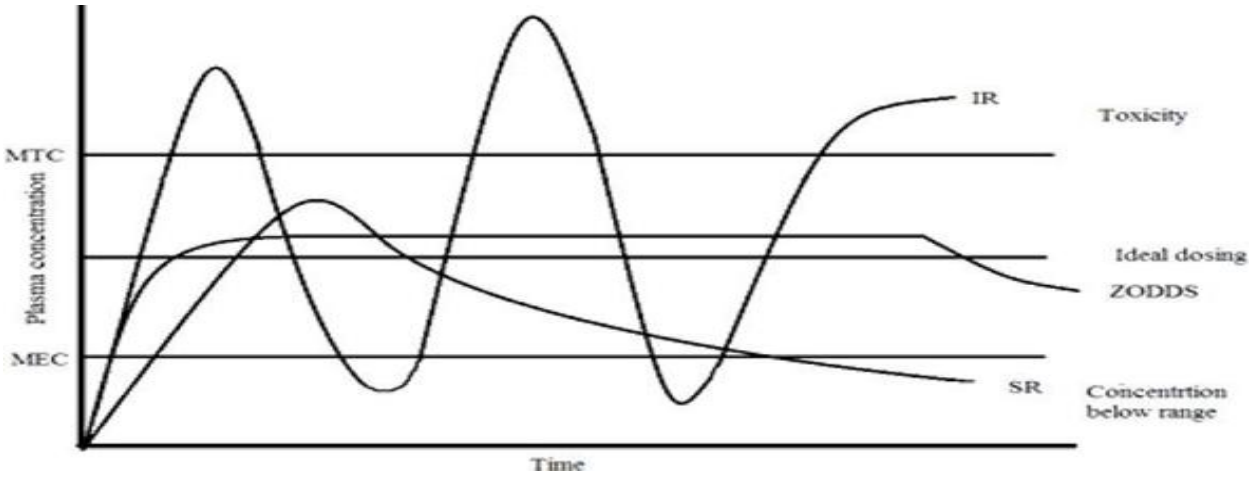


Figure: 1. Ideal plasma concentration curves for immediate release, zero order release and sustained release drug delivery system.

The conventional dosage forms deliver the doses frequently so they can be overshoot or undershoot the therapeutic window. This reduces the effectiveness of the drug and can produce the toxic effect. Sustained-release systems follows zero-order release through a slow first release.

On the other hand, a sustained release system delivers a therapeutic agent at a controlled rate for an extended period of time. Properly considered, it will provide steady-state drug delivery within the therapeutic window. Normally, it follows zero-order kinetics. It may also target drug action by spatially targeting the drug at the site.

(Figure No. 1.2) shows a hypothetical plasma concentration profile of the drug versus time for conventional, controlled, and sustained drug delivery techniques[5].

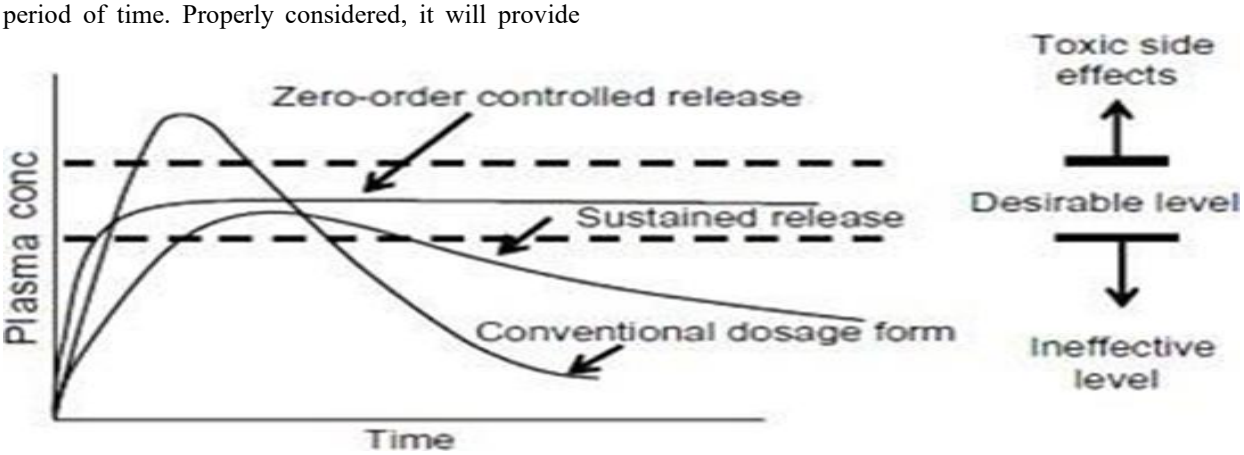


Figure 2: Plasma drug concentration versus time for zero-order controlled release, sustained release and release from conventional dosage forms

Advantages of Sustained release drug delivery system

a) The frequency of drug administration can be reduced
b) Improved patient compliance.
c) The sustainable blood level can maintain.
d) Controlled drug absorption

Disadvantages of Sustained release drug delivery system

a) Increased cost than conventional dosage form
b) Rapid withdrawal of action is not possible.
c) Difficulty in dose adjustment of drugs
d) More rapid development of tolerance

Immediate Release Tablets

Immediate release tablets are those which disintegrate rapidly and get dissolved to releasethe medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. This term excludes formulations which arc adapted to provide for "modified". –controlled "sustained" prolonged", "extended" or "delayed" release of drug. Release term includes the provision (or presentation) of drug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. For gastrointestinal tract release, the release is under pH conditions such as pH=1 to 3, especially at, or about, P

Ideal Properties

1) It should dissolve or disintegrate in the stomach within a short period In the case of solid dosage
2) Should show first absorption and dissolution of drug
3) Rapid onset of action always seen with immediate release tablets
4) Must be compatible with taste masking
5) It should be portable without fragility concern

Advantages:

1) Improved stability, bioavailability
2) Decreased is integration and dissolution times for immediate release oral dosage forms
3) Suitable for controlled, sustained release actives.
4) High drug loading is possible
5) Ability to provide advantages of liquid medication in the form of solid preparation

Disadvantages

- Frequent dosing is necessary for drug with short half-life.
- Drug release at a time may produce high plasma concentration which may produce toxicity.

Drug Selection Criteria for Immediate Release tablets

The immediate release compositions comprise micronized drug in an amount sufficient to provide the desired daily dosage, that is, an amount of about 10 mg to about 1000 mg, more preferably an amount of about 20 mg to 400 mg. 11, 18 Immediate release compositions from which about 50% of the micronized drug is dissolved in vitro within about 15 minutes, more preferably at least about 80% of the drug is dissolved in vitro within about 30 minutes. Carrier materials for immediate release compositions preferably are selected to provide a disintegration time less than about 30 minutes, preferably about 20 minutes or less, more preferably about 18 minutes or less.

Excipients for immediate release tablet :

Bulking Materials in Fast Melting Tablets

Functions:

1. Diluent: Adds bulk to the formulation. 2. Filler: Enhances tablet size and weight.

3. Cost reducer: Reduces the overall cost of the formulation.

Benefits:

1. Improved disintegration: Enhances disintegration in the mouth.

2. Textural characteristics: Improves the texture of the tablet.

3. Reduced active concentration: Decreases the concentration of the active ingredient in the composition.

Recommended Bulking Agents:

1. Sugar-based agents:
   1. Mannitol
   2. Polydextrose
   3. Lactitol
   4. Direct compressible lactose (DCL)
   5. Starch hydrolysates

Characteristics:

1. High aqueous solubility: Enhances dissolution and disintegration.

2. Good sensory perception: Provides a pleasant taste and mouthfeel.

Mannitol:

1. High aqueous solubility: Quickly dissolves in the mouth.

2. Good sensory perception: Provides a sweet and cooling sensation.

Concentration:

1. Range: 10% to 90% by weight of the final composition.

2. Optimization: The concentration of bulking agents can be optimized to achieve the desired disintegration and dissolution profile.

Importance:

1. Critical component: Bulking agents play a crucial role in the formulation of fast melting tablets.

2. Patient compliance: Enhances patient compliance

by providing a pleasant taste and mouthfeel.Emulsifying Agents and Disintegrants in Immediate Release Tablets

Emulsifying Agents:

1. Importance: Aid in rapid disintegration and drug release.
2. Function: Stabilize immiscible blends.

Disintegrants:

1. Cross-linked Povidone (Crospovidone):
- Concentration: 2-5% of tablet weight.
- Mechanism: Water wicking, swelling, and deformation recovery.
- Properties: Insoluble in water, rapid dispersion and swelling.

2. Low-substituted Hydroxypropyl Cellulose:
- Concentration: 1-5%.
- Mechanism: Rapid swelling in water.
- Properties: Insoluble in water, provides binding properties while retaining disintegration capacity.

3. Cross-linked Carboxymethyl Cellulose Sodium (Croscarmellose Sodium):
- Mechanism: Wicking due to fibrous structure, swelling with minimal gelling.
- Effective Concentrations:
  1. 1-3% for direct compression.
  2. 2-4% for wet granulation.

Extended-Release Tablets

Oral Extended-release drug delivery medication will continue to account for the largest share of drug delivery systems. Hence, in this work to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate extended release The extended-release formulations are the type of formulations which will improves the therapeutic index of drug concentration. These formulations make the drug available over extended time period after oral administration.

Drug Selection Criteria for Extended-Release tablets:

Physiochemical Properties of the drug

Aqueous Solubility

Lower limit solubility for such product is reported to be 0,1 mg/ml As the drug must be in solution form before absorption, drug having low aqueous solubility usually' suffers oral bioavailability problem due to limited GI transit time of undissolved drug and limited solubility at absorption site. So these types of drugs are undesirable. Drug having extreme aqueous solubility are undesirable for ER because, it is too difficult to control release of drug from the dosage form. Physiological ph. dependent solubility i.e. variation in solubility at different GI PH are undesirable (e.g. Aspirin, which is less soluble in stomach, but more soluble in intestine) as it will yield variation in dissolution rate.

Partition Co-efficient As biological membrane is lipophilic in nature through which the drug has to pass though, so partition co-efficient of drug influence the bioavailability of drug verymuch. Drug having lower partition co-efficient values less than the optimum activity are undesirable for oral ER drug delivery system, as it will have very less lipid solubility and the drug will be localized at the first aqueous phase it comes in contact e.g. Barbituric acid. Drug having higher partition co- efficient value greater than the optimum activity are undesirable for oral ER drug delivery system because more lipid soluble drug will not partition out of the lipid membrane once it gets in the membrane.

Drug Stability in-vivo as most of ER Drug delivery system is designing to release drug over the length of the GIT, hence drug should be stable in GI environment. So, drug, which is unstable, can't be formulated as oral ER drug delivery system, because of bioavailability problem. e.g. - Nitro- glycerin.

Protein Binding the Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes ER drug delivery system is not required for this type of drug.

Drug pKa & Ionization at Physiological pH As we know only unionized drug are absorbed and permeation of ionized drug is negligible, since its rate of absorption is 3 to 4 times less than that of the unionized drug. PKa range for acidic drug where ionization is ph. I sensitive is around 3.0 - 7.5 and pKa range for basic drug whose ionization is pH at the site to an extent 0.1-5.0%. Drugs existing largely in ionized form are poor candidates for oral ER drug delivery system. e.g.: - Hexamethonium.

Mechanisms and Sites of Absorption Drug absorption by carrier mediated transport and those absorbed

through a window are poor candidate for oral ER drug delivery system e.g.-several B vitamins. Drugs absorbed by passive diffusion, pore transport and through over the entire length of GIT are suitable candidates for oral ER drug delivery system.

Molecular Size and diffusivity with large molecular size are poor candidate for oral ER drug delivery system because it the ability of the drug to diffuse polymeric membrane is a function of its diffusivity (or diffusion co-efficient). Diffusivity depends on size shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug i.e.- 100 to 400 Dalton, through flexible polymer range from 10- 6 to 10-9 cm2/sec.

Dose Size If a product has dose size >0.5g it is a poor candidate for oral ER drug delivery system, because increase in bulk of the drug, thus increases the volume of the product.

Concentration dependency on transfer of drug Transfer of drug from one compartment to other by zero kinetic process then such drugs are poor candidate for oral ER delivery system it should be first order kinetics.

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.

Bilayer Tablets

Bilayer tablets are composed of two layers of direct compressed together. Two-layer tablets require fewer materials than compression- coated tablets weigh less and may be thinner. Monograms and other distinctive marking may be impressed in the surface of multilayer tablets. Coloring the separate layers provide many possibilities for unique tablet identity. Separation of the layers prior to assay may simplify the analytical work. Since there is no transfer to a second set of punches and dies, as with the dry coating machine, odd shapes (such as triangles, squares and ovals) present no operating problems except for those common to keyed tooling.

Bilayer tablets: -Quality and GMP requirements

1. Single sided tablet press
2. Double sided tablet press
3. Bilayer tablet press with displacement monitoring

- Ideal characteristics of bilayer tablets A bi- layer tablet should have elegant product
- identity- while free of defects like chips, cracks. Discoloration and contamination.
- A bi-layer tablet should have sufficient strength to withstand mechanical shock during its production packaging. shipping and dispensing,
- It should have the chemical and physical stability to maintain its physical attributes over time. The bilayer tablet must be able to release the medicinal agents in a predictable and reproducible manner.

Hypertension

Hypertension, defined as a persistent raised blood pressure of 140/90mmHg, is one of the most common disorders in the UK. although it rarely causes symptoms on its own, the damage it does to the arteries and organs can lead to considerable suffering and burdensome healthcare costs. Hypertension is arguablythe most important modifiable risk factor for coronaryheart disease (the leading cause of premature death in the UK) and stroke (the third leading cause). It is also an important cause of congestive heart failure (heart strain) and chronic kidney disease. This has earned hypertension a reputation as the silent killer, making it a key priority for prevention, detection and control, and one of the most important challenges facing public healthy today. Hypertension is high blood pressure, that is, a resting systemic. Consistently above the normal range (90 to 120/60 to 80 mm/Hg). Clinician now consider 125 to 139/85 to 89 mm/hg to be prehypertension. A systolic reading of 140 to 159 mmHg or a diastolic reading of 90 to 99 mm/hg Ir. May be called stage 1 hypertension, and a systolic reading above 160 mm/hg or diastolic reading above100 mm/Hg may he called stage 2 hypertension, the term "essential hypertension" means that no specific cause can be determined; most cases are in this category, For some people, however, an overproduction of renin by the kidneys is the cause of their hypertension.

Five main types of hypertensions 1) Essential (or primary): accounts for 95% of cases of hypertension in the UK. No specific underlying cause but thought to result from a genetic predisposition in addition to the cumulative effects of various lifestyle factors e.g. salt intake, physical inactivity.

2)Secondary: accounts for up to 5% of cases. Caused by an underlying disease, most commonly chronic kidney disease, or as a side-effect of medication.

3)Malignant (or accelerated): a very high or rapidly rising

blood pressure which threatens end-organ damage and requires urgent or emergency treatment. About 1% of those with essential hypertension develop malignant hypertension.

4)Ge st ation al: occurs during pregnancy and usually returns to normal following childbirth.

5)White-coat: occurs when a person's blood pressure is high when they see a doctor or nurse, but is 'normal' at other times.

Dependence on medications by following certain guidelines:

1) Don't smoke, because nicotine stimulates vasoconstriction. Which raises BP. Smoking also damages arteries, contributing to arteriosclerosis.
2) Lose weight if overweight. A weight loss of as little as 10 pounds can lower BP. A diet high in fruits and vegetables may. For some people. Contribute to lower BP.
3) Cut salt intake in half. Although salt consumption may not be the cause of hypertension. Reducing salt intake may help lower blood pressure by decreasing blood volume.

II. MATERIAL AND EQUIPMENT

Various material and equipment's were used to carry out the experimental work. The list of material and equipment used are given in the table no. 5.1 & 5.2

Sr. No.	Material	Sources
1.	Propranolol	Concept pharma Aurangabad
2.	HPMC-15 m	ɒratories Ltd, Nagpur
3.	Microcrystalline cellulose	chem limited, Mumbai
4.	Ethyl cellulose	emie Pvt.Ltd., Mumbai
5.	HPMC-100 C	chem limited, Mumbai
6.	Sodium starch glycolate	emie Pvt.Ltd., Mumbai
7.	Polyvinyl-pyrrolidone	chem limited, Mumbai
8.	Mg. stearate	ɒratories Ltd, Nagpur
9.	Talc	chem limited, Mumbai

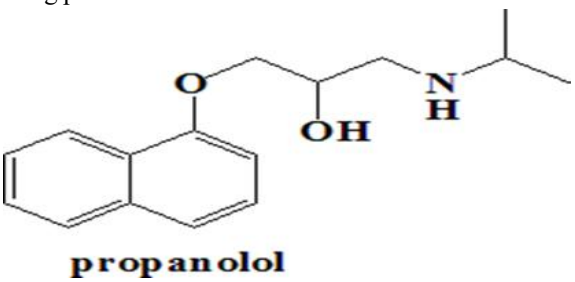
Table no 1 . List if material used in formulation.

Table No 2 . List of equipment used in formulation.

Sr. No.	Equipment	Source
1.	Digital weighing balance	Sartorius
2.	Tablet machine	ıchinery co. Pvt Mumbai
3.	Monsanto hardness tester	Dolphin Mumbai
4.	tion test apparatus (eight stages)	Electro lab Mumbai
5.	spectrophotometer single beam	ıt Cary 630 ATR FTIR spectrophotometer
6.	pH meter	Hanna instrument
7.	Vernier caliper	Mututoyo, japan
8.	Stability chamber	Skylab, Mumbai
9.	IR	ıt Cary 630 ATR FTIR spectrophotometer
10.	Roche friabillator	Electro lab
11.	Stability chamber (106 Model	LABTOP, SKY Lab Instruments and Engineering Pvt. Ltd.

DRUG AND EXCIPIENT PROFILE

Drug profile



Propranolol

IUPAC Name1-(Isopropylamino)-3-(1-naphthyloxy)-2- propanolol

Chemical name Propranolol Molecular formul $C_{16}H_{22}C_1NO_2$ Average weigh 259.3434
Melting point 158-164^{0}C
Water solubility 61.7 mg/ml (at 25^{0}C)

Permeability -4.58
pKa 9.42
Color white powder
Odour Odourless
Solubility Practically insoluble in ether, benzene, ethyl acetate
Biological half-life 2-3 hr.
Blood protein binding 80-95%

Mechanism of action: Propranolol Hall competes with sympathomimetic neurotransmitters like as Catecholamine's for binding at beta (1)-adrenergic receptors in the heart, inhibiting sympathetic stimulus. This consequences in a decrease in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension. Among factors that give to the antihypertensive action are: (1) reduced cardiac output, (2) inhibition of rennin discharge by the kidneys, and (3) decrease of tonic sympathetic nerve outflow from vasomotor centres in the brain .

Pharmacokinetic and metabolism

Absorption Propranolol HCL is entirely absorbed following oral administration. Bioavailability: 30%. Volume of distribution: 3-5 l/kg; 2.8 l/kg. Propranolol HCL has the maximum degree of lipid solubility, compared with other β-blockers, which enables it to enter the BBB and to gather in the brain. Elimination half-life: 2 to 3 hrs, extended up to 14 hrs. At the overdose.

Metabolism: Propranolol HCL is entirely metabolized. It is efficiently extracted during the first pass during the liver, where it is bio-transformed, with the production of several active metabolites. One of them is 4-hydroxypropranolol, which has β-blocking activity similar to that of propranolol HCL and is present in plasma after oral administration of the drug, but has a lesser half-life than a parental drug

Excretion About 84-92% of an oral dose is excreted in the 48 h urine, with 20% as naphthoxylactic acid, up to 25% as propranolol glucuronide and only about 0.5% of the unchanged drug.

Pharmacodynamics Propranolol HCL is the example of the beta-adrenergic receptor antagonists' drug. It is a competitive, nonselective beta-blocker like to nadolol without intrinsic sympathomimetic action. Propranolol HCL is a racemic compound, their l-isomeric form is accountable for adrenergic blocking action.

Therapeutic uses

In the management of the Angina pectoris (with the exception of variant angina), Tachyarrhythmia, Hypertension, Tachycardia (and other sympathetic nervous system symptoms, Myocardial infarction, such as muscle tremor) allied with diverse conditions, including anxiety, panic, hyperthyroidism, and lithium therapy.

Dose Adult:

sustained-release formulation: 40 mg orally 2 times a day or 80 mg orally once a day, used for adult person

Adverse effects

Due to the high penetration across the blood-brain barrier, lipid soluble beta blockers such as propranolol are cause sleep disorder such as vivid dreams, wakefulness and nightmares.

Drug interaction

Clinically significant interactions particularly occur with: Verapamil, levosalbutamol, formoterol, salmeterol, clenbuterol, Quinidine, Clonidine, Ergot alkaloids, Isoprenaline (isoproterenol), Nonsteroidal anti-inflammatory drugs (NSAIDs), Cimetidine, Lidocaine, Phenobarbital, Epinephrine (adrenalin), β2-adrenergic receptor agonists, Salbutamol, Rifampicin, Fluvoxamine (slows down the metabolism of propranolol HCL significantly, leading to increased blood levels of propranolol HCL 18-19

Excipient profile

1. Hydroxypropyl methyl cellulose (HPMC)
2. Microcrystalline cellulose (MCC
3. Polyvinyl-pyrrolidone K30 (PVP)
4. Sodium starch Glycolate (SSG)
5. Tak
6. Ethyl cellulose

III. EXPERIMENTAL WORK

Pre-formulation study

Pre-formulation may be described as a phase of the research & development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the Pre- formulation phase begins early in the discovery process such the appropriate physical, chemical data is available to aid the selection of new chemical entities that enter the development process during this evaluation possible interaction with various inert ingredients intended for use in final dosage form are also considered in the present study

Organoleptic properties:

1.Color: A small quantity of propranolol HCL powders were taken in butter paper and viewed in well-illuminated place.

2.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.

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. If the sample is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Tare a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Put the sample in the bottle, replace the cover, and accurately weigh the bottle and the contents. By gentle, sidewise shaking, distribute the sample as evenly as practicable to a depth of about 5 mm.Place the loaded bottle in the drying chamber. Dry the sample at the specified temperature for constant weight. Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator before weighing.

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

Solubility Analysis:

1. Solubility: The approximate solubility's of substances are indicated by the descriptive terms in the accompanying table. 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 of Solute
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 equipment. 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 n-octanol as the organic phase and distilled water as the aqueous phase. Accurately weighed 10 mg amount of drug was taken in the glass stoppered separating funnel containing 10 ml of n-octanol and 10 ml of water. The mixture was set aside for 24 hrs. At room temperature with intermittent shaking. The two phases were separated and diluted. Thereafter, the drug concentration in aqueous phase and n-octanol phaseswas determined spectrophotometrically Results are shown

5. Flow properties (Angle of Repose):

The angle of repose of granules was determined by funnel method. The funnel was fixedat a particular height (2.5 cm) on a burette stand. The powder sample was passed through the funnel untilit forms a pile. Further adding of granule was stopped as soon as the pile touches the tip of the funnel.A circle was drawn across it without disturbing the pile. The radius of the pile was noted down. Thesame procedure was repeated for three times andthe average value was taken. The angle of repose was calculated by using equation:

$\tan \theta = h/r$ (or) $\theta = \tan^{-1}(h/r)$

Where, h and r are the height and radius of the powder cone.

Table No: 3 Angle of repose as an indication of granule flow properties

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

1) Bulk density: (D_b)Procedure:

Weighed quantity of Propranolol HCL were transferred into a 50ml measuring

$$D_b = m/Vo$$

cylinder without tapping during transfer the volume occupied bygranules was measured.

Bulk density (D_b) was measured by using formula.

Where, m: Mass of the blend

vo: Untapped Volume

2) 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.

$$D_t = m/Vi$$

Where,

m: Mass of the blend

Vo: Untapped Volume

3) Measurement of Powder Compressibility:

1) Compressibility Index:

The compressibility index of the granules was determined by the Carr's compressibility index

Tapped density– poured density Carr's index (%) = 10

Table No: 4 Carr's index as an indication of granule flow properties Tapped 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

2) Determination of Hausner ratio**:** It is measurement of frictional resistance of the drug. It was determined by the ratio oftapped density and bulk density.

$$\text{Hausner Ratio} = Vo/Vi$$

Where, Vo: Tapped density

Vi: Untapped No: 7.3 Hausner's ratio as an indication of granule flow properties

Analytical methods

- Standard curve of propranolol HCL

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

Standard solutions (10µg/ml) of propranolol HCL were prepared, in 0.1 N HCL, phosphate buffer pH6.8, and phosphate buffer pH 7.4. The prepared solutions were scanned on UV spectrophotometer for the determination of absorption maxima (λ-max).

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

10 mg of propranolol HCL was dissolved in 100 ml of 0.1 N HCL to get stock solution of 100 µg/ml concentration. This stock solution was suitably diluted to get graded solutions in the range of 10- 80µg/ml. The absorbance of each solution was determined by using UV spectrophotometer at wavelength of 289 nm (λ-max). Shown in table

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

10 mg of propranolol HCL was dissolved in 100 ml of phosphate buffer of pH 6.8 to get stock solution of 100 µg/ml concentration. This stock solution was suitably diluted to get graded solutions in the range of 10-80µg/ml. The absorbance of each solution was determined by using UV spectrophotometer at wavelength of 288 nm (λ-max). Shown in table

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

10 mg of propranolol HCL was dissolved in 100 ml of phosphate buffer of pH 7.4 to get stock solution of 100 µg/ml concentration. This stock solution was suitably diluted to get graded solutions in the range of 10-80µg/ml. The absorbance of each solution was determined by using UV spectrophotometer at wavelength of 288 nm (λ-max). Shown in table

- Dose calculation

Following formula was used to calculate initial dose of propranolol HCL for immediate release layer of bilayer tablets.

Dt = Initial Dose (1 + 0.693 × t/t 1/2) Where

Dt = total dose of drug, t = time,

t 1/2 = Half-life of drug

Half-life of propranolol HCL is 4 hrs. Hence by using above formula the initial dose of propranolol HCL was calculated.

Formulation of sustained release bilayer tablets

Sustained release bilayer tablets of propranolol HCL were formulated by using natural and modified polymers as release retardant materials by direct compression and wet granulation method.

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

Bilayer tablets of propranolol HCL contained two types of layers i.e. immediate release layer and second sustained release layer. The Immediate release layer prepared, by using starch and PVP. Sustained release layer consist of the different concentration of polymer as release retardant materials. Bilayer sustained release tablet of propranolol HCL were formulated by using direct compression and wet granulation methods. Composition of immediate release layer and sustained release layer are shown in Table no.7.4

Table No: 5 Composition of propranolol HCL immediate release layer

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: 6 Composition of propranolol HCL sustained 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	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg

- Blends preparation of immediate release layer for direct compression method

The Propranolol layer was prepared by using direct compression method. All the ingredients except magnesium Stearate and Aerosil were passed through sieve No: 40, weighed and mixed for 15 mints and finally blended well in ascending order of their weights. Magnesium Stearate and Aerosil were passed through sieve No: 60 and mixed it to the above blend. Finally colorant was added and blended uniformly and compressed in a 16 station automatic punching machine with a punch size of 10 mm. composition of propranolol HCL immediate release layer is shown in table 7.4

- 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. Then the sieved blend was transferred to a poly bag and mixed for 5 minutes. The magnesium stearate as lubricant was added and mixed again for 2 minutes98. Composition of propranolol HCL sustained release layer is shown in Table No: 7.5

2. Pre-compression evaluation of blends

Blends of immediate release layer and sustained release layer for both direct compression and wet granulation methods were evaluated for pre-compression parameters like Angle of repose, Bulk density g/cm3, Tapped density g/cm3, Carrs index and Hausner ratio. Composition of blends is given in Table no. 4.3 and 4.4.

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. It represents the bulk volume of the blends powder or granule. After this the volume of the blends powder or granule was examined after every 50 taps up to a total of 300 taps. It represents the tapped volume of the blends powder or granule. The bulk density and tapped density were calculated using the following formula.

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.

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

Where, Vtρ= tapped density; Vρ= bulk density

4)Angle of repose

The flow properties of blend of powder were determined by 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. Angle of repose was calculated by following formula:

$$\theta = \tan -1(h)\ r$$

Where, h= height of pile;

r= radius of the base of the pile and θ = angle of repose.

A clean and dry funnel was fixed with burette stand at

height of 6 cm. A graph paper was placed on the flat surface and 10 gm of the blend was permissible to flow slowly through the funnel until the pile touched the tip of the funnel. The circumference of the heap was drawn and the midpoint was placed and its radius was measured. The experiment was repeated thrice and the average height and radius were calculated. The angle of repose was calculated by using above formula.

Compression of propranolol HCL bilayer tablets by direct compression method

First, the die was filled with sustained release blend and compressed using single punch tablet compression machine equipped with 10 mm round concave punches. Upon this compressed sustained release layer, accurately weighted quantity of immediate release layer blend was transferred. Then compression was carried out again to get bilayered tablet.

Evaluation of sustained release bilayer tablets

1) Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in

Table No 7 : Weight variation Limit

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

2)Hardness test

The resistance of tablets to shipping or breakage under conditions of storage, Transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

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. Friability was calculated using the formula

Friability (%) = $W1-W2$ W1

Where, w1 was the initial weight of tablets before friability testing, w2 was the weight of tablets after the test

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.

Dissolution studies

Drug Release Studies for Immediate release layer

The in vitro dissolution of immediate release layer was determined using USP XXIII (basket method) dissolution apparatus. The basket was allowed to rotate at a speed of 100 rpm and temperature of 37 ± 0.5°C was maintained. The dissolution medium used was 900 ml of 0.1N HCL (pH 1.2) for 2 hours. Aliquots (5 ml) of sample were collected at predetermined time intervals (5, 10, 15, 20, 25 and 30min) from the dissolution apparatus and it was replaced with equal volume of fresh dissolution

medium. The aliquots withdrawn were filtered through 0.45µm millipore filters.

Drug Release Studies for sustained release layer:
The in vitro dissolution of sustained release layer was determined using USP XXIII (basket method) dissolution apparatus. The basket was allowed to rotate at a speed of 100 rpm and temperature of 37 ± 0.5°C was maintained. The dissolution medium used was 900 ml of 0.1N HCL (pH 1.2) for the initial 2hours followed by study in simulated intestinal fluid Phosphate buffer solution (pH 6.8). Aliquots (5 ml) of sample were collected at predetermined time intervals (1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 hrs) from the dissolution apparatus and it was replaced with equal volume of fresh dissolution medium. The aliquots withdrawn were filtered through 0.45µm millipore filters.

Drug Release Studies for Bilayer Tablets:
The in vitro dissolution of Propranolol bilayer tablets were determined using USP XXIII (basket method) dissolution apparatus. The basket was allowed to rotate at a speed of 100 rpm and temperature of 37 ± 0.5°C was maintained. The dissolution medium used was 900 ml of 0.1N HCL (pH 1.2) for the initial 2hours followed by study in simulated intestinal fluid Phosphate buffer solution (pH 6.8). Aliquots (5 ml) of sample were collected at predetermined time intervals (1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 hrs. from the dissolution apparatus and it was replaced with equal volume of fresh dissolution medium. The aliquots withdrawn were filtered through 0.45µm millipore f

Table No. 8 Details data of dissolution test

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

Mathematical Modeling of Drug Release Profile Models Used:
1. Zero-Order Kinetics:

- Equation: At = A0 - K0t
- . Plot: Cumulative % drug release vs. time
- Linearity: Indicates zero-order release kinetics
- Slope: Equal to K0 (zero-order rate constant)

2. First-Order Kinetics:

- Equation: Log cumulative % drug remaining vs. time
- Plot: Log cumulative % drug remaining vs. time
- Linearity: Indicates first-order release kinetics
- Constant: K (first-order rate constant) = 2.303 x slope

3. Higuchi Model:

- Equation: Not explicitly mentioned, but typically Q = KH * t^0.5
- Plot: Cumulative % drug release vs. square root of time

4. Korsmeyer-Peppas Model:

- Equation: Mt/M∞ = Kt^n
- Plot: Log (Mt/M∞) vs. log time
- Mechanism: Helps understand the release mechanism (Fickian or non-Fickian diffusion)

Stability Studies
Definition:
Stability of a drug: The ability of a formulation to remain within its physical, chemical, therapeutic, and toxicological specifications over time.

Purpose:
1. Assess quality variation: Evaluate how environmental conditions (temperature, humidity, light) affect the quality of the drug formulation.
2. Determine storage conditions: Establish recommended storage conditions, re-test periods, and shelf-life.

Importance:
1. Uniform dose assurance: Manufacturers ensure patients receive a consistent dose throughout the shelf life.
2. Regulatory compliance: Drug control administrations require stability studies to ensure identity, strength, purity, and quality.

IV. RESULT AND DISCUSSION

Pre-formulation studies
Characterization of propranolol HCL
Organoleptic Properties:

Table No 9 Organoleptic characterizations of propranolol HCL

Test	Observations
Colour	White crystalline powder
Taste	Bitter salty
Odour	odourless

Physical characteristic:

Loss on Drying:
Table No10 . Loss on Drying

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

Angle of Repose

Table No.11 Angle of Repose of Bulk Drug

Sr.no.	Material	Angle of repose	Average angle of repose
1.	Propranolol HCL	28º·37’	28^0.56’
2.		29º.17’	
3.		28º14’	

Determination Bulk density and Tapped density:

Table No: 12 Determination of Bulk density and Tap 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	

Compressibility and Hausner’s ratio

Materials	Compressibility index	Hausner ratio
Propranolol HCL	22.64	1.34

solubility properties:
Solubility study of drug (PRP) was performed in 0.1N HCL, distilled water; phosphate buffer pH 7.4 and results are presented in Table. The solubility of propranolol HCL was found to be 0.1 N HCL (138.27±0.1mg/ml), distilled water (58.32±0.4 mg/ml) and buffer pH 7.4 (145.80±0.2 mg/ml) indicating that it is soluble in water

ph. of the solution:

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

Melting point

It is one of the parameters for the determination of purity of any drugs. In case of pure chemicals compounds, melting points are very sharp and constant. The average melting point was noted 158-1640C for the drug propranolol HCL and recorded values are shown in Table

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

Partition Coefficient

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

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

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

Analytical methods:

Standard curve of propranolol HCL (λ max) 1 Calibration curve of propranolol hydrochloride using HCL (pH 1.2) The calibration curve of propranolol HCL was prepared using 0.1N HCL pH 1.2, phosphate buffer, pH

6.8 and 7.4, by using Ultraviolet–visible (UV) spectroscopy. The absorbance was determined at 287 nm for different concentrations in the range of 10, 20, 30, 40, 50µg/ml as reported in Table 8.5 and shown in Figures 8.1 and 8.2. A high degree of correlation (R^2 = 0.999) was observed between the concentration of the drug solution and their respective absorbance obtain.

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

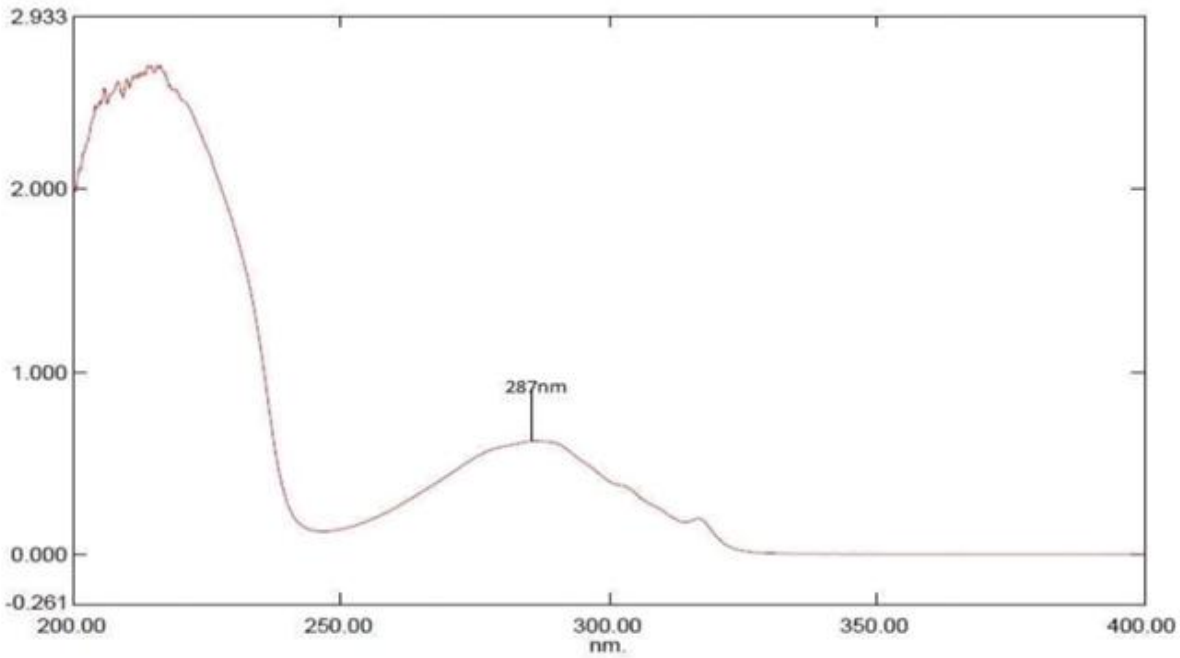


Table No: 13 . Calibration curve of propranolol HCL using 0.1N HCL (pH 1.2)

S. 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

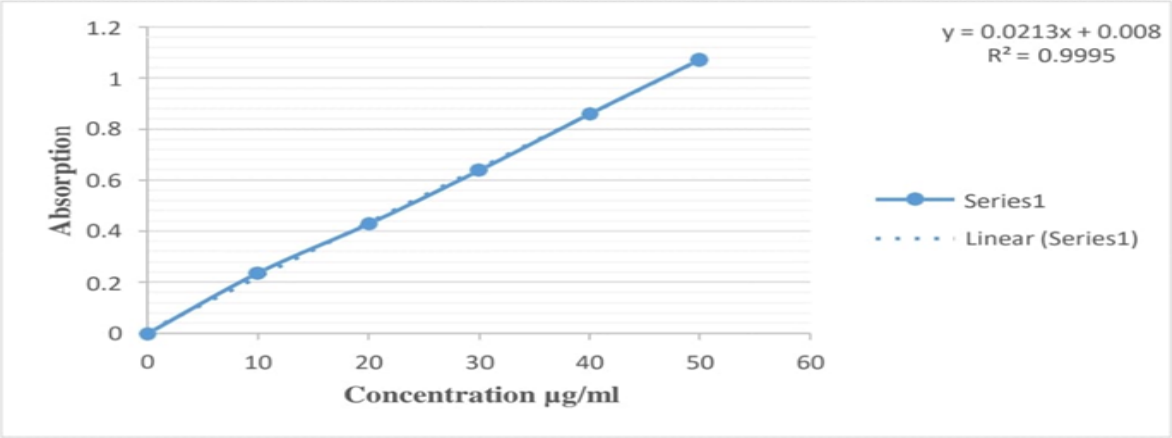


Figure No: 4 . Standard curve of propranolol HCL using 0.1N HCL (pH 1.2)

The calibration curve of propranolol HCL was prepared in phosphate buffer, pH 6.8 byusing UV spectroscopy. The absorbance was determined at 288 nm for different concentrations in the range of 10, 20, 30, 40, 50µg/ml as reported in Table 8.6 and shown in Figures 8.3 and 8.4. A high degree of correlation (R^2 = 0.996) was observed between the concentration of the drug solution and their respective absorbance obtained.

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

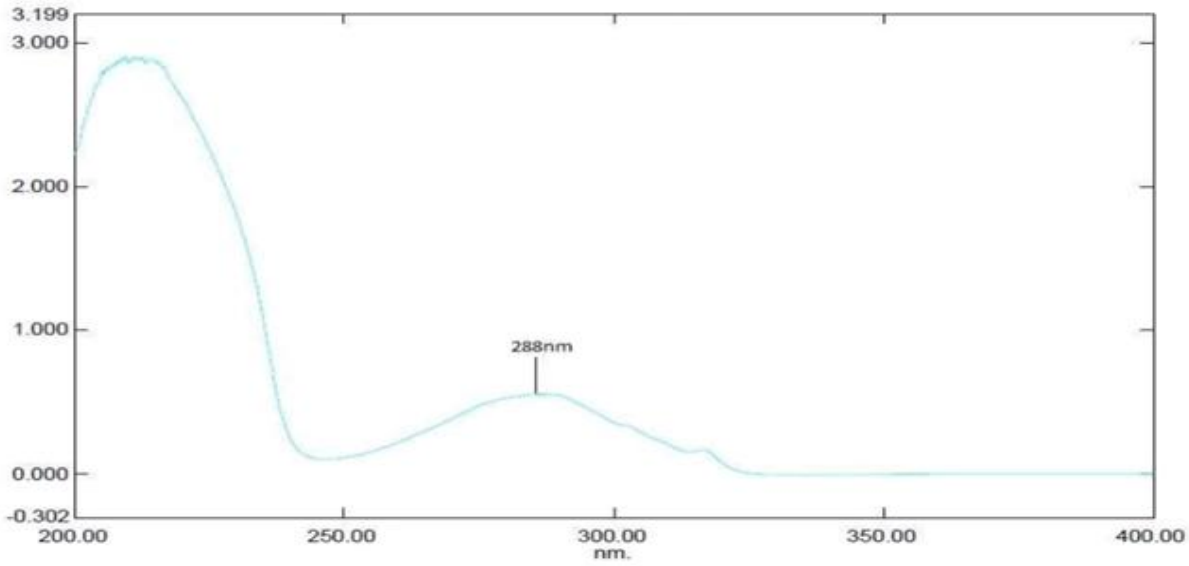


Table No: 14 Calibration curve of propranolol HCL using phosphate buffer (pH 6.8)

S. 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

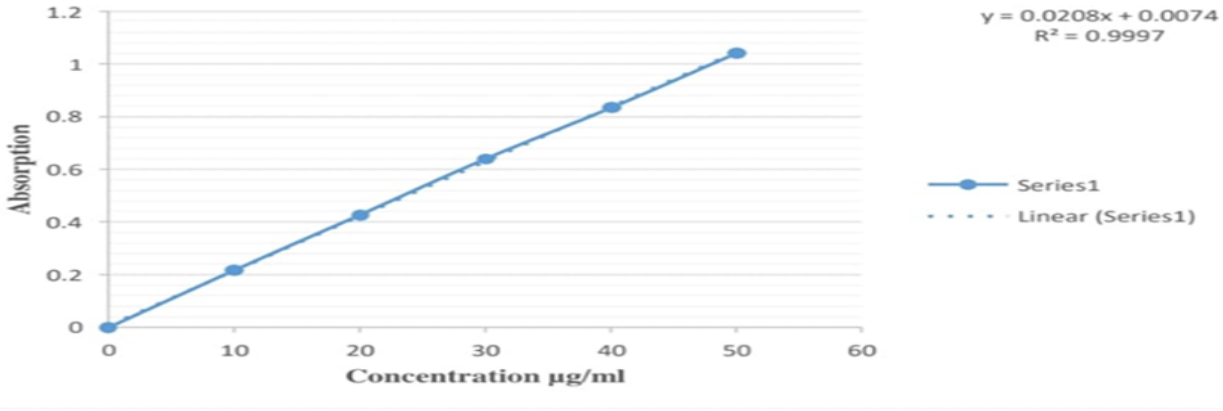


Figure No: 6 . Standard curve of propranolol HCL using phosphate buffer (pH 6. 8)

Calibration curve of propranolol HCL using phosphate buffer (pH 7.4)

The calibration curve of propranolol HCL was prepared in phosphate buffer, pH7.4 by using UV spectroscopy. The absorbance was determined at 288nm for different concentrations in the range of 10, 20, 30, 40, 50µg/ml as reported in Table 8.7 and shown in Figures 8.5 and

8.6. A high degree of correlation ($R^2 = 0.999$) was observed between the concentration of the drug solution and their respective absorbance obtained

Figure No: 7 . UV curve of propranolol HCL using phosphate buffer (pH 7.4)

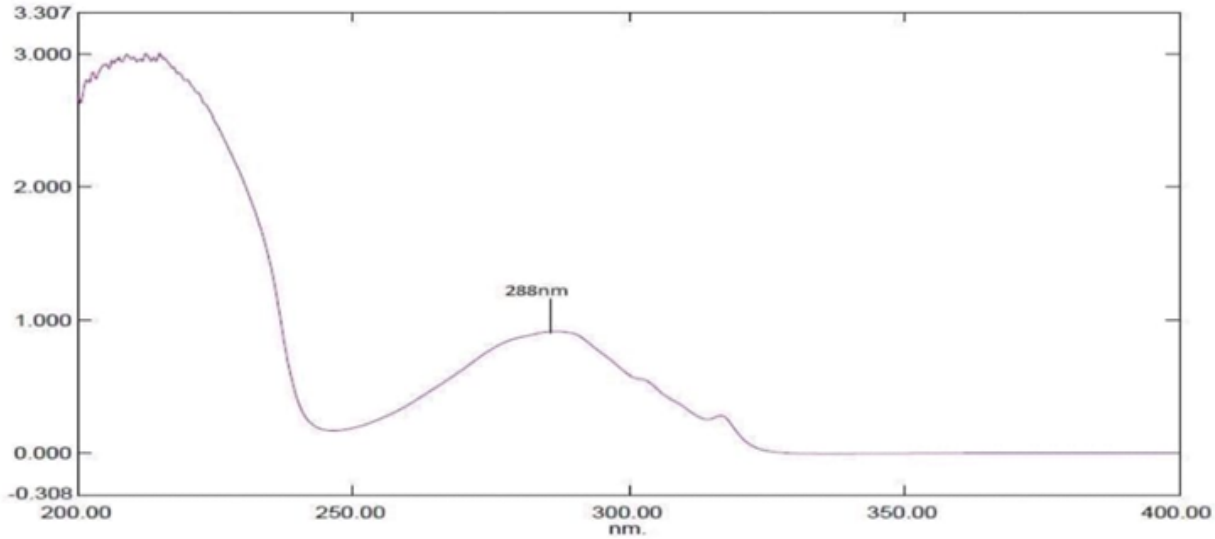


Table No: 15 Calibration curve of propranolol HCL using phosphate buffer (pH 7.4)

S. No.	Concentration µg/ml	Absorbance
1.	0	0
2.	10	0.217
3.	20	0.428
4.	30	0.641
5.	40	0.835
6.	50	1.042

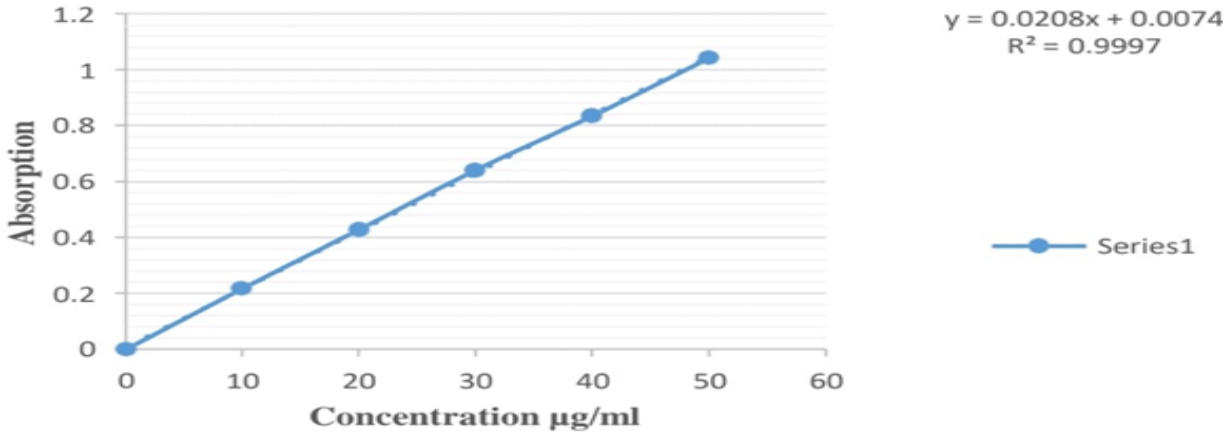


Figure No: 8 . Standard curve of propranolol HCL using phosphate buffer (pH 7.4)

Fourier Transform infrared spectroscopy:

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 are shown in Table No. 5.10 and Figure 5.13.

Table No: 16 . FTIR interpretation of propranolol HCL

FTIR range of peak (cm-1)	Presence of functional groups in 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

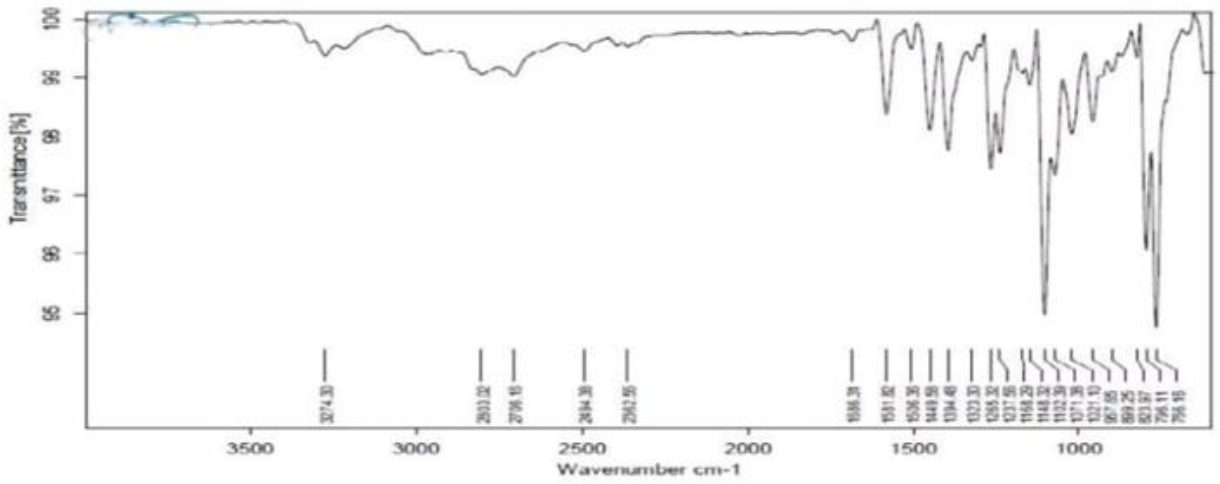


Figure No: 9 . FTIR spectra of propranolol HCL

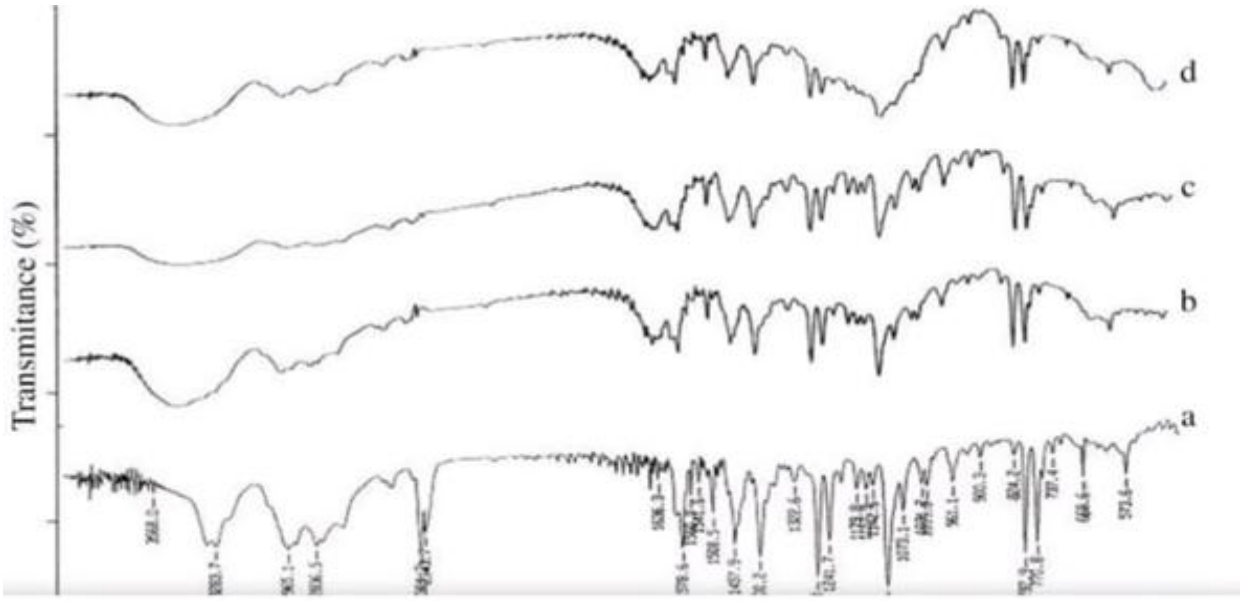


Figure No. 10 . FTIR spectra of propranolol (a), propranolol with ethyl cellulose (b), propranolol with HPMC K15(c), Propranolol with HPMC K100 (d).

All the characteristic peaks of Propranolol were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. From 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 drug- polymer physical mixtures, indicating that they were compatible chemically. The spectrum confirmed that there is no significant change in the chemical integrity of the drug.

Prepared Bi-layer sustained release Anti-hypertensive Tablet:

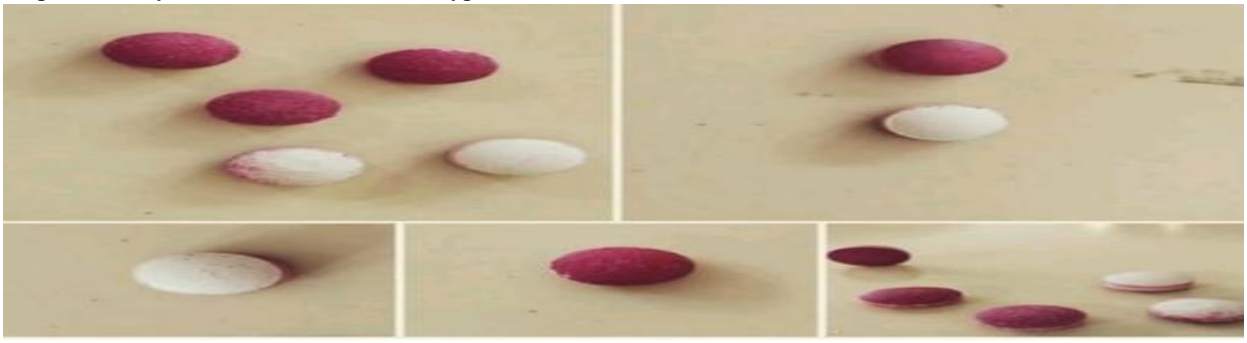


Fig No.11 . Prepared Bi-layer sustained release Anti-hypertensive Tablets

Evaluation Parameters: Evaluation of powder blended characteristics of Bilayer tablet formulation of Propranolol

For each type of formulation, blends of propranolol and other excipients were prepared and evaluated for various parameters such as bulk density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose. 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 & 7.27-18.42 % and 1.053-1.24 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 & 25.33-31.43° for sustained release. The results of angle of repose showed all powder blends exhibited good to acceptable flow property. The results of pre-compression parameters are shown in table no:

Formulations Number	lk Density (gm/cc)	pped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	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

Post-compression parameters

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

Formulation	Diameter (mm)± SD	Thickness (mm)± SD	Weight variation (mg)	Hardness (kg/cm2)	ability (%)	tegration time	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

From the above observation it was found that IR 3 shows good result. So it will be use Table No: 19 . standard physical tests for Bilayer tablets

Formulation	Diameter (mm)± SD	Thickness (mm)± SD	Weight variation (mg)	Hardness (kg/cm2)	ability (%)	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

Thickness of tablets: All the formulations were evaluated for their thickness using "Vernier callipers" as per procedure and the results are shown in table no 8.10 the average thickness for all the formulations was found in the range of 3.8-4.2 mm which is within the allowed limit of deviation i.e. 5% of the standard value. Also, the crown diameter of all the tablet formulation was in the range of 8.0-7.8 mm.

Hardness: All the sustained release Bilayer tablet formulations of propranolol were evaluated for their hardness as per procedure and the results were dissipated in table no: 8.10 Hardness test was performed by "Monsanto hardness tester". All the formulations have an average hardness in between 6.0 to 8.0 kg/cm2. This ensures good Handling characteristics of all formulation batches.

Friability The entire Sustained release Bilayer tablet formulations were evaluated for their percentage friability and the results are shown in table no: 8.10 the average percentage friability for all the formulations was found in between 0.40% to 0.72%, which is found within the pharmacopoeial limit (i.e. less than 1%). So the maximum friability was 0.72% observed for F4 and the minimum friability 0.40.7% observed for F7

Weight variation test: : As the powder material was free-flowing, tablets obtained were uniform in weight due to uniform die fill with acceptable variation as per IP standards. The weight variation for all formulations was found in the range of 249.92 to 253.88 mg and results were dissipated in table no:8.10 All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits (<5%). The weights of all the tablets were found to be uniform with low standard deviation values.

Drug Content: The percentage of the drug content for formulation F1 to F9 was found to be between 96.23%w/w and 99.67%w/w. It complies with official specifications.

In-vitro Drug release studies: n - vitro drug release study of immediate release layer of Propranolol The release profile of Propranolol from different batches of formulated tablets was represented in table no 7.4. Based on the results of in-vitro dissolution testing it was known that all the immediate release layer batches shown the drug release within 20-30 minutes. But the formulation IR-3 shown maximum amount of drug release i.e. 99.10±0.95 % within 15 minutes in a immediate release manner and hence was considered as the best batch to get incorporated in bilayer tablet formulation. From the results of in-vitro drug release studies it was also found that as the concentration of S.S.G. was increasing from 5 % to 10 % the release rate of Propranolol was also increased. This is due to the reason that increased concentration of disintegrant lead to decreased disintegration time and thus increased release of Propranolol

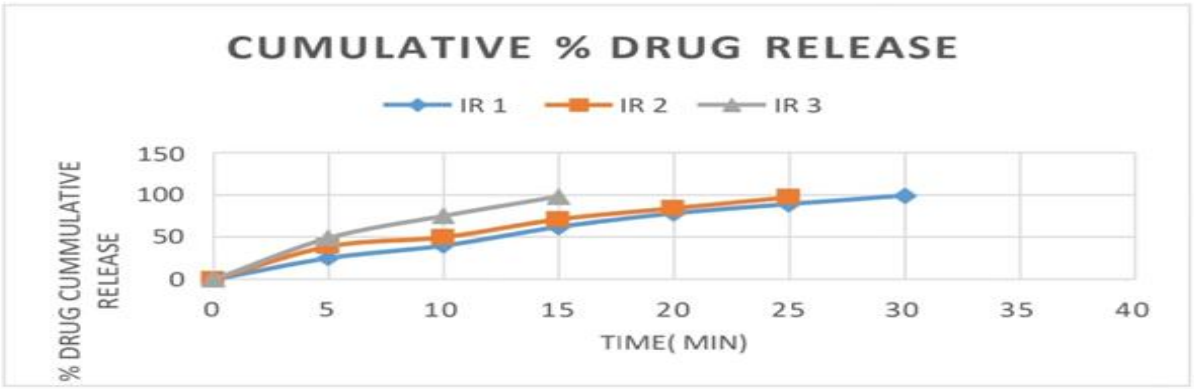


Figure No: 12 . In-vitro disintegration data for IR-1, IR-2, and IR-3 Formulation

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

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		

In - vitro drug release study of Sustained release Bi-layer tablet of Propranolol

The dissolution rate was studied using 900 ml of 0.1 N HCL (ph. 1.2) for first 2 hrs. Followed by phosphate buffer (ph. 7.4) for the remaining hours under sink condition using USP dissolution apparatus type II. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in predetermine manner.

Table No: 21 In-vitro dissolution data of F1, F2, and F3 Formulation

Time (hrs.)	Cumulative percent drug release		
	F1	F2	F3
0	0	0	0
1	25.12±0.09	18.34±0.43	15.38±0.10
2	40.02±0.12	22.10±0.10	20.90±0.45
3	58.75±0.14	29.24±0.33	25.10±0.12
4	72.41±0.81	35.45±0.12	31.46±0.21
5	80.03±0.28	48.71±0.2	46.13±0.13
6	91.61±0.34	59.99±0.54	52.18±0.43
7	99.13±0.41	68.41±0.55	63.97±0.42
8		72.12±0.10	70.33±0.54
9		77.09±0.22	74.50±0.65
10		82.23±0.12	80.96±0.66
11		85.86± 0.26	82.13±0.10
12		95.12±0.33	95.10±0.23
13		97.54± 0.1	98.51±0.12

figure no: 13 In-vitro dissolution profile of F1, F2 and F3 formulation

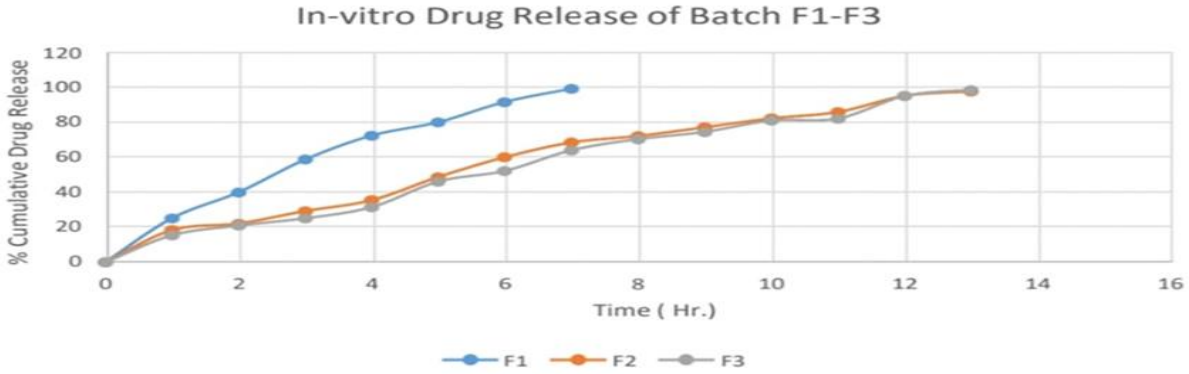


Table No:22. In-vitro dissolution data of F4, F5, and F6 Formulation

Time (hrs.)	Cumulative percent drug release		
	F4	F5	F6
0	0	0	0
1	25.72±0.10	23.81±0.10	21.26±0.8
2	29.99±0.18	28.10±0.7	25.25±0.12
3	41.54±0.9	35.23±0.1	28.10±0.8
4	58.74±0.12	42.12±0.8	32.12±0.12
5	68.72±0.8	50.23±0.1	40.40±0.5
6	81.57±0.12	65.10±0.23	52.13±0.12
7	95.19±0.10	76.70±0.8	61.23±0.8
8	97.17±0.8	84.17±0.6	65.10±0.2
9	98.13±0.4	89.3±0.2	70.53±0.13
10	98.13±0.6	95.2±0.14	78.13±0.5
11		97.5±0.5	85.20±0.1
12			89.54±0.5
13			95.23±0.24
14			98.81±0.9

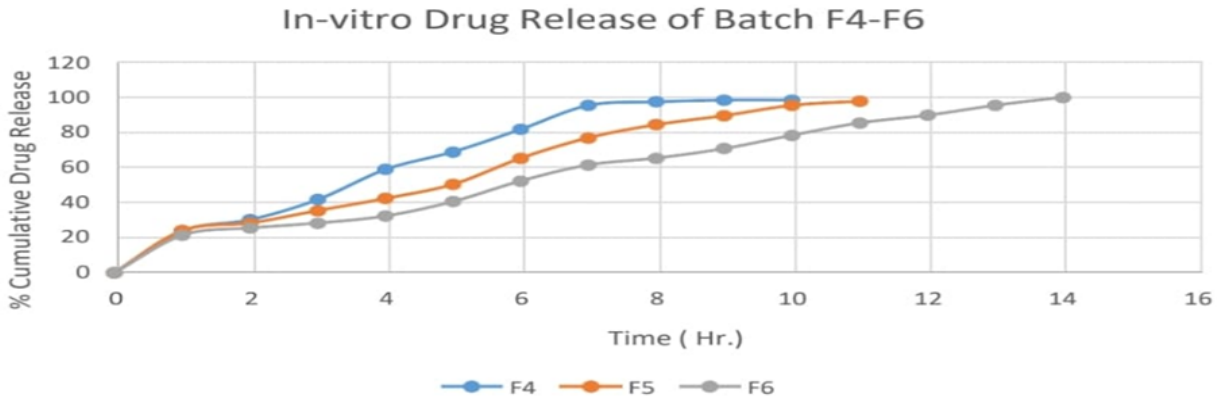


Figure No. 14 In-vitro dissolution profile of F4, F5 and F6 formulation

The release of propranolol hydrochloride from the prepared formulations was analyzed by plotting the cumulative percent drug released *vs*. time as shown in Figs. 8.12–8.14. Simple visual observation of the plot shows an initial burst effect. From all the formulations, over 30% of the propranolol hydrochloride was released within the first 15 min of the dissolution study. This initial high amount of propranolol hydrochloride release can be attributed the immediate release layer of the formulation. Further release of propranolol hydrochloride was studied for 12 h.

Ethylcellulose has been used as release retardant polymer in controlled release dosage forms. EC reduces the drug release due to a reduction in the penetration of the solvent molecules into the system because of the hydrophobic nature of ethylcellulose present on the surface of the tablet, *i.e.* the rate of release is controlled by the permeability of bilayer structure

Release Kinetics:

The in-vitro release of drug data for the formulations of PRP sustained release bilayer tablets prepared by direct compression method were fitted to different kinetic models and regression coefficients was calculated. The regression values and rate constants for the formulations of PRP sustained release bilayer matrix tablets prepared by Direct Compression are

presented in table no. Release kinetics for optimized
batch F-9 are given below

Table No:23 . Drug release kinetic studies of Optimized Batch F9 for sustained release bilayer tablets

	Zero Order	First Order	Hixon Crowell	se meyer peppas model	Higuchi Plot
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

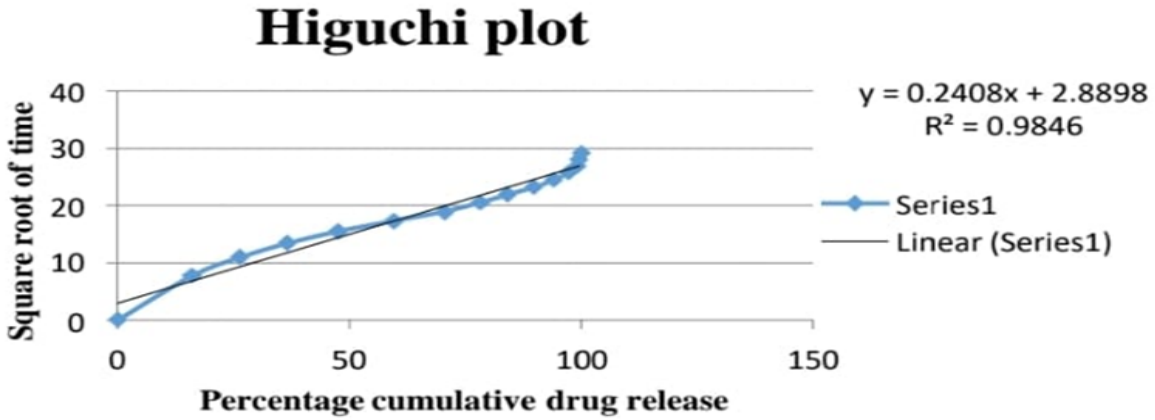


Fig no: 15 Drug release kinetic studies of Optimized Batch F-9

Stability studies:

Based on the results of in-vitro drug release two best formulations F6 and F9 were selected for stability studies at 25ºC/60% RH and at 45ºC/75% RH. The stability studies were conducted according to the method described in section four. The selected formulations were evaluated for physical appearance, hardness, friability, and drug content and in-vitro drug release. The results showed that there was no significant change in physical appearance, hardness, friability, drug content and drug release profile throughout the study period. Three Months of stability studies revealed that; there was no any significant degradation of the drug. Thus prepared formulations were physically and chemically stable. The result of stability studies were tabulated in table no

Table No:24 Results of stability studies for formulation F9 stored at 25ºC/60% and 45ºC/75%RH

Storage period	Stored at 25ºC/60% RH			Stored at 45ºC/75% RH		
	Formulation F9			Formulation F9		
	Hardness Kg/cm2	% friability	% Drug content	Hardness Kg/cm2	% friability	% Drug content
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 15 days	6.5±0.16	0.57±0.3	99.6±0.1	6.4±0.11	0.55±0.1	97.5±0.3

IV. CONCLUSION

Propranolol is beta blocker that is, it blocks the action of epinephrine (adrenaline) and norepinephrine (noradrenaline) at both β1- and β2-adrenergic receptors, which in turn results in reduced blood pressure and is used in treatment of hypertension. The objective of the present study was to investigate the

possibility of sustaining the propranolol release from bi-layer tablet prepared by using different concentration of polymers.

The following conclusions can be drawn from the result obtained.

- The pre-formulation studies like angle of repose, bulk density, tapped density Haunser's ratio and Carr's index of all formulations were found to be within the standard limits.
- FTIR studies revealed that there was no chemical interaction between drug and other excipients.
- The powder mixtures were compressed into tablet and evaluated for post-compression parameters like weight variation, thickness, hardness, friability and drug content. All the formulation batches showed acceptable results.
- The in-vitro drug release was studied with USP Type-II dissolution apparatus in bothsimulated gastric fluid and intestine fluid for a period of 24 hours. Results showed that formulations containing higher concentration of HPMC K15 M i.e. F6 (99.12%) and HPMC k100 i.e. F9 (99.67%) sustained the drug release over a period of 24 hours.
- The in-vitro drug release follows first order and indicated that non-Fickian could be the mechanism of drug release.
- Stability studies showed that the tablets formulations were stable throughout the stability period.
- It was concluded that the polymer plays a major role in the formulation of sustain release bilayer tablets of propranolol. Finally, the study revealed that the release of drug was low when the bilayer tablet contained higher concentration of polymers.

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