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DEVELOPMENT OF FORMULATION AND IN VITRO EVALUATION OF GASTRO RETENTIVE FLOATING DRUG DELIVERY SYSTEM FOR PINDOLOL BILAYER TABLETS

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ABSTARCT

The present study was carried out for developing the formulation of Floating bilayer tablets of Pindolol. IR layer was compressed as direct compression method and SR layer blends were compressed by wet granulation method. IR and SR Layers were evaluated for pre and post compression studies. Those all studies were found to be within limits. From the dissolution data of Pinodolol Immediate release Layer, IR4 formulation was shown maximum drug release at 20min. i.e., 96.58%. Hence IR4 was concluded as optimised formulation for IR layer. From the dissolution data of floating bilayer tablets of Pindolol, B2 (IR4&SR2) has shown good drug release. SR2 contain Carbopol 940(Synthetic Polymer). Formulations containing Eudragit S100 and L 100 retard the drug release more than 12 hours hence those formulations did not take into consideration. B19 formulation was shown best drug release (**97.88%)** within 12 hours which contains Caragennan(Natural polymer). Finally Concluded that B19 formulation was optimised formulation. B19 Formulation contains IR4 immediate release and SR19 sustained release formulation blend. SR19 which follows zero order release kinetics.

KEYWORDS: Pindolol, IR layer, Direct compression, SR floating layer, Wet granulation method, Floating bilayer tablets.

Aim of the Work

The aim of the study is to formulate and evaluate gastro retentive floating bilayer tablets of Pindolol by effervescent method.

Objective of the Study

The main objective of this study.

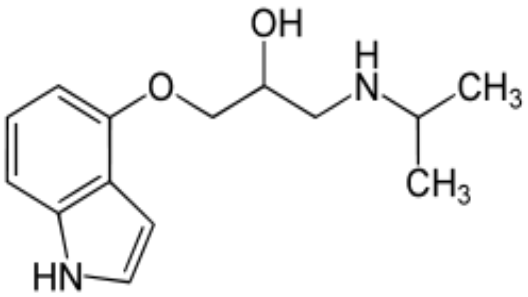
1) The present research work aims to develop a bilayer floating tablet of Pindolol
2) To carry out the drug-Excipient compatibility studies.
3) To evaluate the drug release in developed formulations by in-vitro studies.

DRUG PROFILE

Name : Pindolol

Description : A moderately lipophilic beta blocker (adrenergic beta-antagonists). It is non-cardioselective and has intrinsic sympathomimetic actions, but little membrane-stabilizing activity.

Structure



Chemical Name : [2-hydroxy-3-(1H-indol-4-yloxy)propyl](propan-2-yl)amine

Molecular Formula : $C_{14}H_{20}N_2O_2$

Molecular Weight : 248.3208 gram/mole

Appearance : Solid

Solubility : Water solubility-7880 mg/L

Melting Point : 171^0C

PKa : 9.67

Category : Beta blocker

Pharmacokinetic Data

Absorption : Rapidly and reproducibly absorbed (bioavailability greater than 95%).

Protein Binding : 40%

Metabolism : Hepatic

Half-life : 3 to 4 hours

Excretion : Renal

Mechanism of Action : Pindolol non-selectively blocks beta-1 adrenergic receptors mainly in the heart, inhibiting the effects of epinephrine and norepinephrine resulting in a decrease in heart rate and blood pressure. By binding beta-2 receptors in the juxtaglomerular apparatus, Pindolol inhibits the production of renin, thereby inhibiting angiotensin II and aldosterone production and therefore inhibits the vasoconstriction and water retention due to angiotensin II and aldosterone, respectively.

Uses : For the management of hypertension, edema, ventricular tachycardias, and atrial fibrillation.

Side Effects : Dizziness, drowsiness, weakness, and nausea may occur as your body adjusts to the medication. This drug may reduce blood flow to your hands and feet, causing them to feel cold.

Table 5.1 Marketed Products

S No	Brand Name	Manufacturers	Dosage form	Strength
1	Visken	Novartis	Tablets	10mg, 15mg.

CROSPOVIDONE

Nonproprietary Names

BP: Crospovidone, PhEur: Crospovidone, USP-NF: Crospovidone.

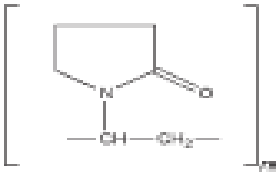
Synonyms

Crospovidonum; Crospopharm; crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL.

Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Structural formula:



Functional Category

Tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Description

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse

effects associated with crospovidone. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.

LD50 (mouse, IP): 12 gm/kg

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

5.2 SODIUM STARCH GLYCOLATE

Nonproprietary Names :BP: Sodium Starch Glycolate, PhEur: Sodium Starch Glycolate, USP-NF: Sodium Starch Glycolate

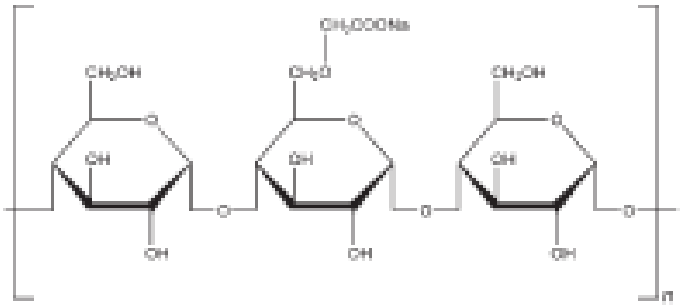
Synonyms

Carboxymethyl starch, sodium salt; carboxymethylamylum natricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar .

Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

Structural Formula



Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is

sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The PhEur 6.0 states that when examined under a microscope it is seen to consist of: granules, irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded, 10–35 mm in size; compound granules consisting of 2–4 component occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum; small crystals are visible at the surface of the granules. The granules show considerable swelling in contact with water.

Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.

Safety

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are

recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

5.3 CARBOPOL

Nonproprietary Names

BP:Carbomers

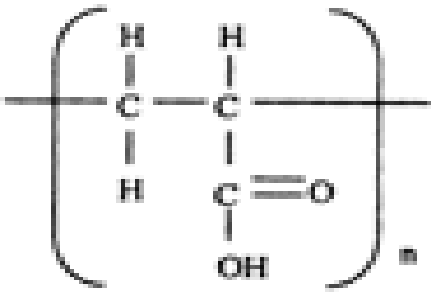
PhEur:Carbomera

USPNF:Carbomer

Synonyms

Acritamer; acrylic acid polymer; Carbopol; carboxypolymethylene, polyacrylic acid; carboxyvinyl polymer

Structural Formula



Carbomer polymers are formed from repeating units of acrylicacid. The monomer unit is shown above. The polymer chainsare crosslinked with allyl sucrose or allylpentaerythritol.

Description

White, fluffy powder, having a slight characteristic odour.Is hygroscopic. The pH of 1 in 100 dispersion is about 3.

Solubility

When neutralized with alkali hydroxyls or with amines, it dissolves in water, in alcohol and in glycerin.

Functional Category

Bioadhesive, emulsifying agent, release-modifying agent, suspending Agent, tablet binder, viscosity-increasing agent.

Pharmaceutical Applications

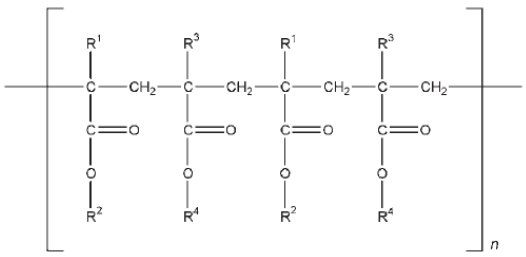
- Carbomer are mainly used in liquid or semisolid pharmaceutical formulations and solid dosage forms as suspending or viscosity-increasing agents.
- Carbomer 934P, 971P, 974P may be used in oral preparations, in suspensions, tablets or sustain release tablet formulations.
- In tablet formulations, carbomers are used as dry or wet binders and as a rate controlling excipients.
- Carbomer resins have also been investigated in the preparation of sustained, release matrix beads, as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms, in oral mucoadhesive controlled drug delivery system.
- Carbomers are also employed as emulsifying agents in the preparation of oil-in-water emulsions for external use.
- Carbomers are also used in cosmetics.

5.4 EUDRAGIT

Synonyms

Acryl-EZE; acidi methacrylici et ethylis acrylatis polymerisatum; acidi methacrylici et methylis methacrylatis polymerisatum; ammonio methacrylatis copolymerum; copolymerum methacrylatis butylatibasicum; Eastacryl; Eudragit; Kollicoat MAE; polyacrylatis dispersio 30 per centum; polymeric methacrylates.

Structure:



Functional Category: Coating agent; flavoring agent; tablet binder; tablet filler; viscosityincreasing agent.

Description: White powders with a faint characteristic odour.

Solubility: 1 g of eudragit® L 100 or eudragit® s 100 dissolves in 7 g methanol, ethanol, in aqueous isopropyl alcohol and acetone (containing approx. 3 % water), as well as in 1 n

sodium hydroxide to give clear to cloudy solutions. eudragit ® l 100 and eudragit® s 100 are practically insoluble in ethyl acetate, methylene chloride, petroleum ether and water.

Stability and Storage: Minimum stability dates are given on the product labels and related Certificates of Analysis. Storage Stability data are available upon request. Store at controlled room temperatures (USP, General Notices). Protect against moisture. Any storage between 8 °C and 25 °C fulfils this requirement.

Incompatibilities: Incompatible with paraffin wax and microcrystalline wax.

5.5 SODIUM BICARBONATE

Non-proprietary names: BP/EP: sodium bicarbonate

Synonym: Baking soda, e-500, and monosodium carbonate.

Chemical name: carbonic acid, monosodium salt, monosodium carbonate.

Empirical formula: NaHCO3

Molecular weight: 84.01

Category: alkalizing agent, therapeutic agent.

Description: it is an odorless, white crystalline powder with slight alkaline taste.

Acidity/ alkalinity: pH 8.3 for freshly prepared 0.1m aqueous solution at 250c.

Density: 2.159 g/cm3

Solubility: Soluble in water, practically insoluble in ethanol.

Stability and storage: Sodium bicarbonate is stable in dry air but slowly decomposes in Moist air and should therefore be stored in well-closed container in a cool dry place.

Safety: Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence.

Applications:

1. Employed as a source of carbon dioxide in effervescent tablets and granules.
2. Also used to buffer the drug molecules that are weak acids.
3. Used in solutions as buffering agent.
4. Also used as freeze-drying stabilizer.
5. As a gas forming agent.

CROSCARMELLOSE SODIUM

Nonproprietary Name

BP: Croscarmellose Sodium, JP: Croscarmellose Sodium, PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

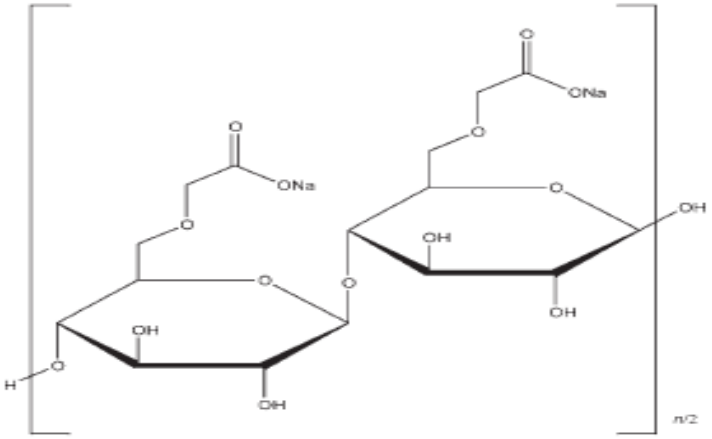
Synonyms

Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, crosslinked.

Structural Formula:



Functional Category: Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extra-granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Use Concentration (%)

Disintegrant in capsules 10–25

Disintegrant in tablets 0.5–5

Description

Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30^0C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Safety

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems. In the UK, croscarmellose sodium is accepted for use in dietary supplements. The WHO has not specified an acceptable daily intake for the related substance carboxymethylcellulose sodium, used as a food additive, since the levels necessary to achieve a desired effect were not considered sufficient to be a hazard to health.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Croscarmellose sodium may be irritant to the eyes; eye protection is recommended.

MICROCRYSTALLINE CELLULOSE

Synonyms : Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460;Emcocel; Ethispheres.

Chemical Name : Cellulose

Empirical Formula : $(C_6H_{10}O_5)n$ where $n \approx 220$.

Molecular Weight: ≈36 000

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

METHODOLOGY

Analytical method development

Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

Preparation calibration curve

10mg of Pindolol pure drug was dissolved in 10ml of methanol (primary stock solution). From primary stock, 1ml of solution was taken and make up with 10ml of 0.1N HCl (100µg/ml) from this secondary stock solution 0.5, 1, 1.5, 2 and 2.5 ml was taken and diluted up to 10 ml with 0.1N HCl to obtain 5, 10 ,15 ,20 and 25µg/ml concentration. The absorbance of the above dilutions was measured at respective wavelength by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550cm^{-1}.

Differential Scanning Calorimetry (DSC)

The possibility of any interaction between the drug and the carriers during preparation of solid dispersion was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture and solid dispersion using DSC. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 350°C under a nitrogen flow of 50 mL/min.

6.3. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of

physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

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

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

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

Table 6.1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula.

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Table 6.2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

6.3. Formulation development of Bilayer floating Tablets:

Immediate layer was prepared by direct compression method and Sustained layer was compressed by wet granulation technique.

Procedure for direct compression method

1) Drug and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Procedure for Wet granulation method:

1) Drug and required ingredients were individually weighed.
2) To that required amount of Isopropyl Alcohol was added to get wet mass.
3) Wet mass was sieved using Sieve # 60.
4) Obtained wet granules were allowed to dry.
5) To dried granules required amount of lubricant and glidant was added and blended up to 15 min.
6) The tablets were compressed using rotary tablet compression machine.

Optimisation of Immediate release Layer

For optimisation of immediate release layer various formulations were prepared as noted in a table.

Table 6.3: Formulations for IR tablets

Ingredients	**IR1**	**IR2**	**IR3**	**IR4**	**IR5**	**IR6**
Pindolol	5	5	5	5	5	5
Croscarmellose Sodium	2.5	5	-	-	-	-
Crospovidone	-	-	2.5	5	-	-
Sodium starch glycolate	-	-	-	-	2.5	5
Mg. Stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	**100**	**100**	**100**	**100**	**100**	**100**

FORMULAITON OF BILAYER TABLETS OF PINDOLOL

Optimisation of Sodium bicarbonate

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating

lag time and floating duration were observed. Based on the concentration of sodium bicarbonate was finalized and preceded for further formulations.

Table 6.4: Optimization sodium bicarbonate concentration

Ingredients	DO1	DO2	DO3	WO1	WO2	WO3
Pindolol	5	5	5	5	5	5
Carbopol 940	15	15	15	15	15	15
PVP K 30	-	-	-	7.5	7.5	7.5
IPA	-	-	-	QS	QS	QS
$NaHCO_3$	7.5	15	22.5	7.5	15	22.5
Citric acid	7.5	7.5	7.5	7.5	7.5	7.5
Colour (Sunset yellow)	2	2	2	2	2	2
Mg.Stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
MCC	116.5	109	101.5	109	101.5	94
Total weight	150	150	150	150	150	150

All the quantities were in mg.

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimised.

Table 6.5: Formulation Of Bilayer Tablets using Synthetic polymers

Ingredients	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**	**B11**	**B12**
Immediate Layer	IR4	IR4	IR4	IR4	IR4	IR4	IR4	IR4	IR4	IR4	IR4	IR4
SUSTAINED LAYER												
	SR1	**SR2**	**SR3**	**SR4**	**SR5**	**SR6**	**SR7**	**SR8**	**SR9**	**SR10**	**SR11**	**SR12**
Pindolol	5	5	5	5	5	5	5	5	5	5	5	5
Carbopol 940	7.5	15	-	-	-	-	-	-	-	-	-	-
Carbopol 934	-	-	7.5	15	-	-	-	-	-	-	-	-
Eudragit L 100	-	-	-	-	7.5	15	-	-	-	-	-	-
Eudragit S100	-	-	-	-	-	-	7.5	15	-	-	-	-
HPMC K15M	-	-	-	-	-	-	-	-	7.5	15	-	-
HPMC K100M	-	-	-	-	-	-	-	-	-	-	7.5	15
PVP K30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
$NaHCO_3$	15	15	15	15	15	15	15	15	15	15	15	15
Citric Acid	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Colour	2	2	2	2	2	2	2	2	2	2	2	2
IPA	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3
MCC	99.5	92	99.5	92	99.5	92	99.5	92	99.5	92	99.5	92
Total weight of SR LAYER	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

All the quantities were in mg

Table 6.6: Formulation Of Bilayer Tablets using Natural polymers

Ingredients	**B13**	**B14**	**B15**	**B16**	**B17**	**B18**	**B19**	**B20**
Immediate Layer	IR4	IR4	IR4	IR4	IR4	IR4	IR4	IR4
SUSTAINED LAYER								
	SR13	**SR14**	**SR15**	**SR16**	**SR17**	**SR18**	**SR19**	**SR20**
Pindolol	5	5	5	5	5	5	5	5
Xanthan gum	7.5	15	-	-	-	-	-	-
Guar gum	-	-	7.5	15	-	-	-	-
Sodium Alginate	-	-	-	-	7.5	15	-	-
Caragennan	-	-	-	-	-	-	7.5	15
PVP K30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
$NaHCO_3$	15	15	15	15	15	15	15	15
Citric acid	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Colour	2	2	2	2	2	2	2	2
IPA	QS	QS	QS	QS	QS	QS	QS	QS
Mg. Stearate	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3
MCC	99.5	92	99.5	92	99.5	92	99.5	92
Total weight of SR LAYER	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table 6.6: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	**Average weight of tablet (mg) (U.S.P)**	**Maximum percentage difference allowed**
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight were accurately weighed, transferred to a 100 ml volumetric flask containing few ml methanol and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with 0.1N HCl. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* Buoyancy studies**

The in vitro buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time

the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT). This study was carried out for SR layer only.

IN VITRO DRUG RELEASE STUDIES

Dissolution study for immediate layer optimisation

900ml of 0.1N HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 1 hour and then the medium 0.1 N HCl was taken and process was continued at 50 rpm. At definite time intervals of 5 ml of the medium was withdrawn, filtered and again 5ml fresh medium was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at respective wavelength using UV-spectrophotometer.

Dissolution study for Bilayer Tablets

The dissolution study of bilayer tablets was performed over a 12 hr period using USP type II (paddle) Dissolution Testing Apparatus (Lab india) 900ml of 0.1N HCl was used as dissolution medium agitated at 50 RPM, at temperature of $37^{o}\pm 0.5^{o}C$. 5 ml samples were withdrawn at 5, 10, 15, and 20 min to estimate the release of immediate release of pindolol and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hrs for estimating Sustained release pindolol. The samples were analyzed at respective wavelength in UV spectrophotometer by keeping the 0.1 N HCl as blank.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F = K_o t$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

F = k t1/2

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$M_t/ M_\infty = K t^n$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

RESULTS AND DISCUSSION

7.1. Analytical Method

Graphs of Pindolol was taken in 0.1N HCl (pH 1.2)

Table no 7.1:Observations for graph of Pindolol in 0.1N HCl

Conc [µg/mL]	Abs
0	0
5	0.139
10	0.284
15	0.44
20	0.578
25	0.702

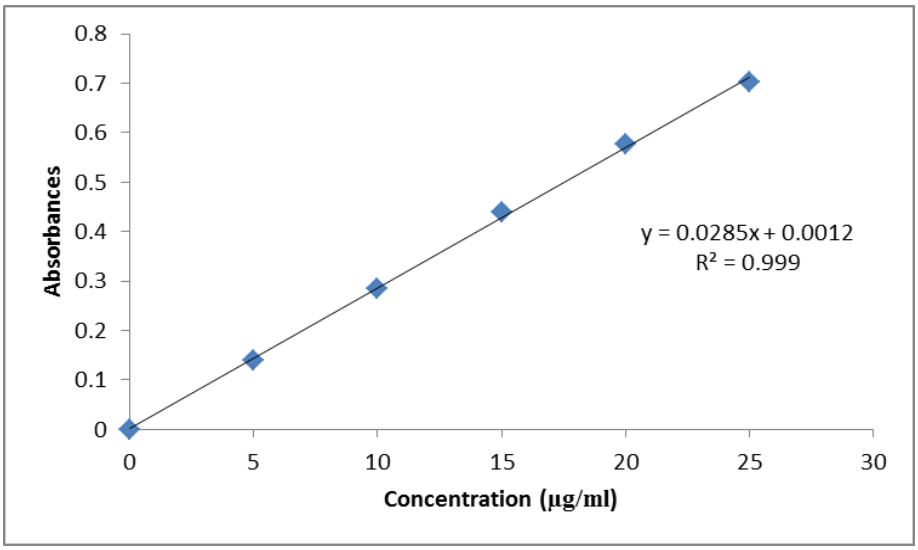


Fig no 7.1:Standard graph of Pindolol in 0.1N HCL

Standard graph of Pindolol was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Pindolol showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

7.2. Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy.

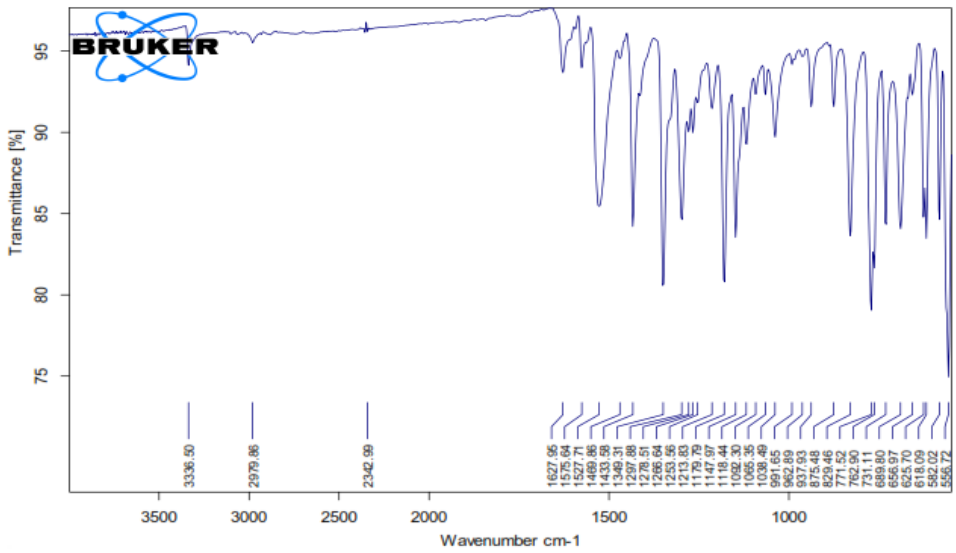


Figure 7.2: FT-IR Spectrum of pure drug.

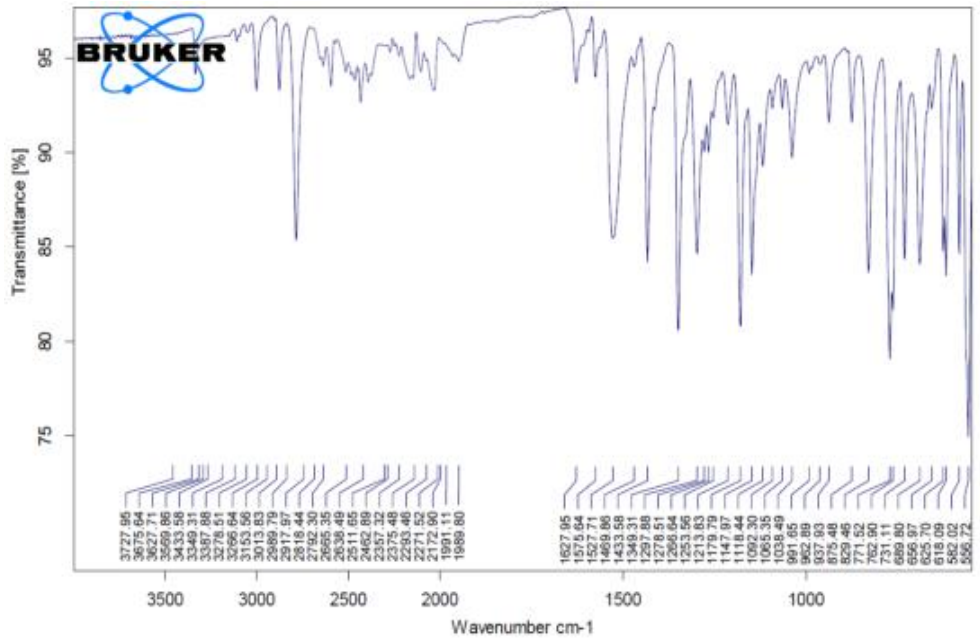


Figure 7.3: FT-IR Spectrum of Optimised bilayer Formulation

There was no disappearance of any characteristics peak in the FT-IR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Pindolol are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

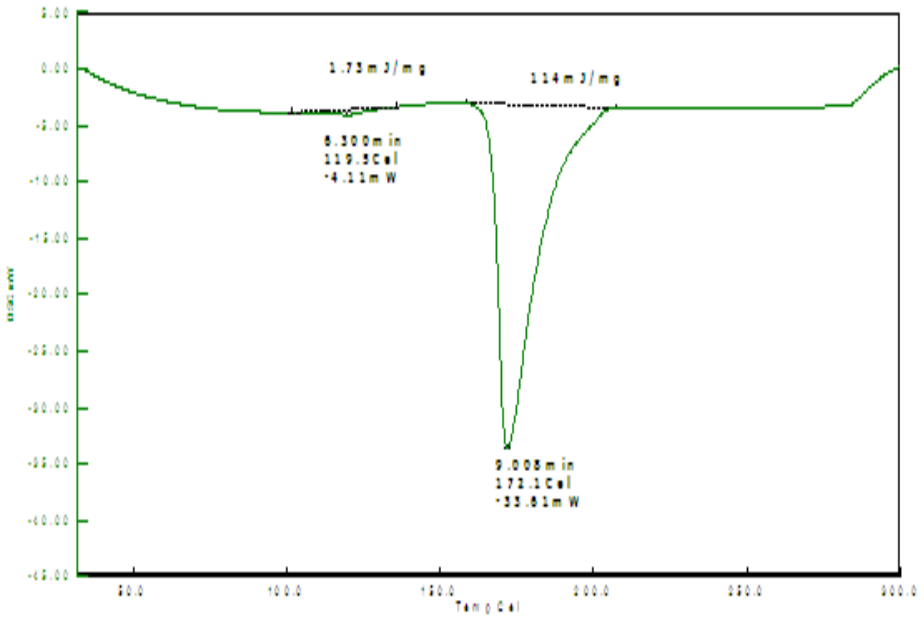


FIGURE : DSC THERMOGRAM OF PURE DRUG

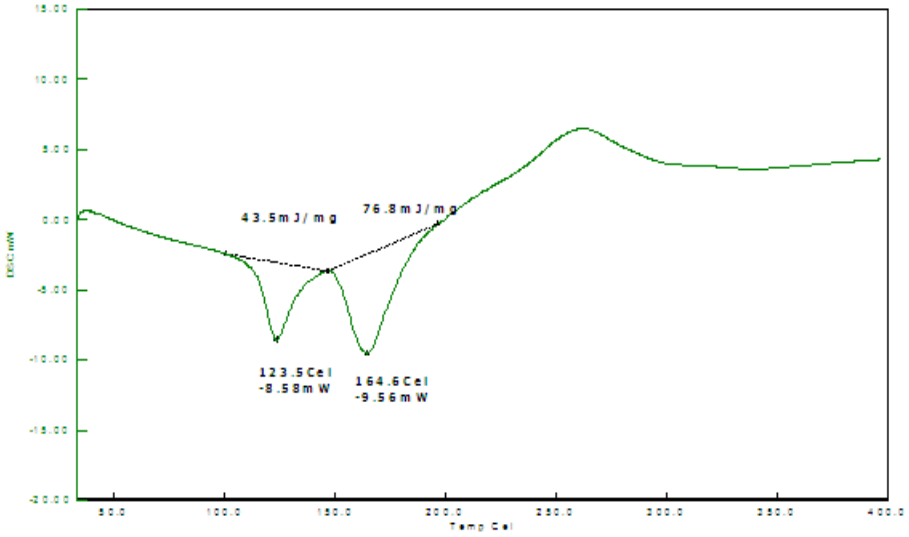


FIGURE : DSC THERMOGRAM OF OPTIMISED FORMULATION

From the DSC studies revealed that there is compatibility between drug and polymers.

7.3. Preformulation parameters of powder blend for Immediate Layer

Table7.2: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
IR1	26.01	0.49	0.57	14.03	1.16
IR2	24.8	0.56	0.65	13.84	1.16
IR3	22.74	0.56	0.68	17.64	1.21
IR4	25.33	0.54	0.64	15.62	1.18
IR5	26.24	0.55	0.67	17.91	1.21
IR6	26.12	0.56	0.66	15.15	1.17

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.49 to 0.56 (gm/mL) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.68 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Preformulation parameters of powder blend for Sustained Layer

Table7.3: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
SR1	25.12	0.59	0.66	11.86	1.11
SR2	26.8	0.48	0.54	12.5	1.12
SR3	23.74	0.56	0.66	17.85	1.17
SR4	26.33	0.44	0.55	18.18	1.18
SR5	25.21	0.48	0.57	16.66	1.16
SR6	27.18	0.51	0.59	15.68	1.15
SR7	24.29	0.46	0.56	17.85	1.21
SR8	26.01	0.50	0.59	15.25	1.18
SR9	25.27	0.44	0.56	16.66	1.21
SR10	25.28	0.41	0.57	15.88	1.21
SR11	26.25	0.42	0.52	16.78	1.21
SR12	23.24	0.44	0.53	15.89	1.21
SR13	23.22	0.47	0.54	15. 45	1.21
SR14	22.28	0.49	0.55	16.66	1.21
SR15	24.89	0.48	0.57	16.66	1.21
SR16	22.38	0.43	0.58	16.66	1.21
SR17	23.98	0.42	0.59	16.66	1.21
SR18	22.59	0.41	0.53	16.66	1.21
SR19	21.47	0.46	0.52	16.66	1.21
SR20	21.39	0.48	0.54	16.66	1.21

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.48 to 0.59 (gm/Cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54 to 0.66 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

7.4. Optimization of sodium bicarbonate concentration for SR Layer

Three formulations were prepared with varying concentrations of sodium bicarbonate by direct compression method and three more formulations were prepared by wet granulation

method to compare the floating buoyancy in between direct and wet granulation methods. The formulation containing sodium bicarbonate in 15mg concentration showed less floating lag time in wet granulation method and the tablet was in floating condition for more than 12 hours.

7.5. Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for IR and SR layer tablets.

Table no: 7.4. *In-vitro* quality control parameters for IR tablets

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
IR1	95.5	2.5	0.52	3.5	99.76
IR2	102.4	2.0	0.54	3.3	97.45
IR3	97.6	2.4	0.51	3.1	98.34
IR4	99.6	2.5	0.55	3.4	99.87
IR5	102.4	2.4	0.56	3.2	99.14
IR6	100.7	2.2	0.45	3.4	97.56

All the parameters for IR layer such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

Table no:7.5. *In- vitro* quality control parameters for SR tablets

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
B1	248.4	5.1	0.61	3.3	98.42	1.5
B2	249.2	5.2	0.58	3.2	99.65	1.4
B3	251.3	5.5	0.45	3.4	99.12	1.0
B4	246.3	5.1	0.61	3.3	98.42	1.5
B5	248.6	5.3	0.59	3.5	99.65	1.4
B6	252.4	5.5	0.65	3.4	99.12	1.3
B7	250.6	5.3	0.62	3.6	98.16	1.2
B8	251.2	5.2	0.59	3.4	98.11	1.3
B9	252.8	5.9	0.34	3.2	99.45	1.3
B10	251.9	5.3	0.26	3.0	99.86	1.3
B11	251.6	5.2	0.29	3.1	99.73	1.2
B12	249.9	5.4	0.45	3.4	99.92	1.1
B13	248.2	5.5	0.87	3.5	99.85	1.1
B14	247.9	5.6	0.65	3.7	99.55	1.9
B15	246.9	5.9	0.47	3.9	99.45	1.8
B16	249.9	5.8	0.58	3.8	99.75	1.7
B17	246.9	5.2	0.69	3.6	99.95	1.6
B18	250.8	5.5	0.73	3.7	99.85	1.5
B19	250.7	5.3	0.87	3.5	99.35	1.4

B20	250.5	5.2	0.59	3.9	99.63	1.2

All the parameters for SR layer such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

7.6. In Vitro Drug Release Studies

Table 7.6: Dissolution data of Immediate release Layer

TIME (Min)	IR1	IR2	IR3	IR4	IR5	IR6
0	0	0	0	0	0	0
5	22.78	30.14	26.38	31.56	10.29	20.38
10	44.56	52.47	41.25	65.98	22.33	40.15
15	61.36	69.63	63.94	86.31	35.81	58.25
20	89.35	85.68		96.58	49.36	69.25
30	98.41	94.16			61.25	86.91
45					76.85	95.66
60					91.02	

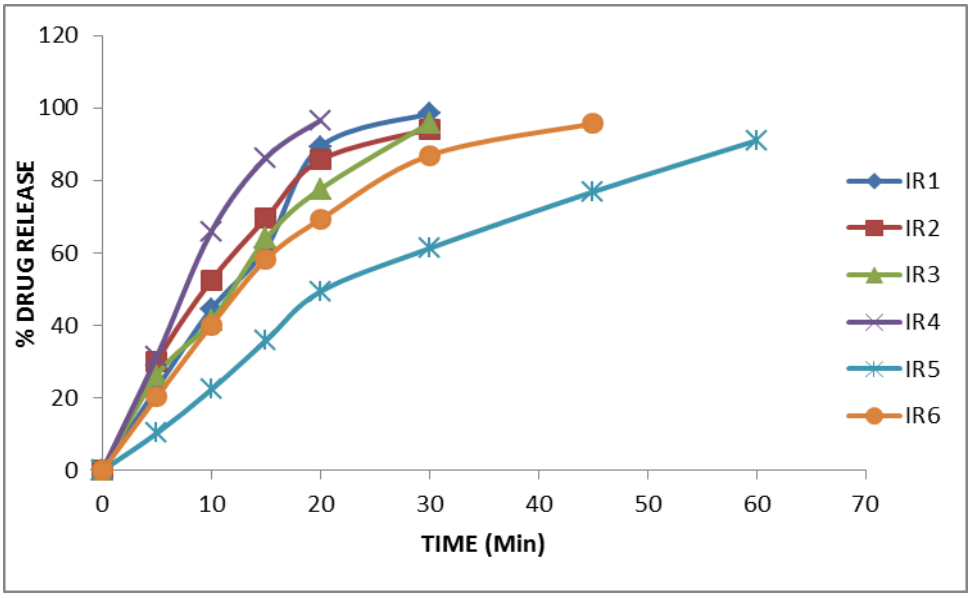


Fig 3 Dissolution data of Immediate release Layer

From the dissolution data of Pinodolol Immediate release Layer, IR4 formulation was shown maximum drug release at 20min. i.e., 96.58%. Hence IR4 was concluded as optimised formulation for IR layer.

Table 4 Dissolution data of Pinodolol Floating bilayer using Synthetic polymers

Time (Min)	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	30.43	31.42	29.34	30.56	29.82	31.56	30.11	34.34	28.67	29.65	32.23	30.54
10	72.61	73.16	59.41	66.13	63.20	67.82	65.47	70.51	68.9	73.34	71.32	69.23
15	93.62	83.36	73.66	88.14	89.14	89.08	86.33	83.62	83.26	92.65	88.98	87.54
20	95.13	96.01	96.14	95.89	95.58	94.11	95.14	96.08	94.26	95.38	96.13	95.76
60 (1 hr)	6.33	5.12	19.63	12.36	9.09	4.32	9.22	7.56	6.89	4.67	6.89	5.38
120 (2 hr)	15.69	12.63	34.63	26.48	13.28	8.66	17.91	8.68	12.86	11.46	10.32	8.98
180 (3 hr)	28.94	19.66	58.24	35.12	29.1	10.15	17.97	9.63	22.38	19.89	12.54	10.76
240 (4 hr)	36.84	26.84	79.63	51.94	34.7	12.94	28.22	21.95	38.9	26.82	15.89	14.98
300 (5 hr)	46.51	33.86	94.62	66.84	36.62	21.03	33.92	27.48	59.35	39.67	26.67	24.78
360 (6 hr)	59.14	43.25		82.65	42.72	26.66	37.35	34.18	62.78	48.32	37.45	33.54
420 (7 hr)	68.34	49.63		96.51	50.73	30.55	44.1	37.32	88.24	52.67	42.64	40.27
480 (8 hr)	79.52	57.65			57.49	37.63	53.34	40.26	97.32	68.22	58.93	56.11
540 (9 hr)	88.45	69.8			62.48	44.17	58.82	44.65		85.65	61.76	60.23
600 (10 hr)	96.37	76.94			72.68	50.82	62.23	51.02			98.68	82.45
660 (11 hr)		84.33			76.39	56.5	68.76	52.37				94.67
720 (12 hr)		**95.10**			84.72	59.83	73.38	58.05				

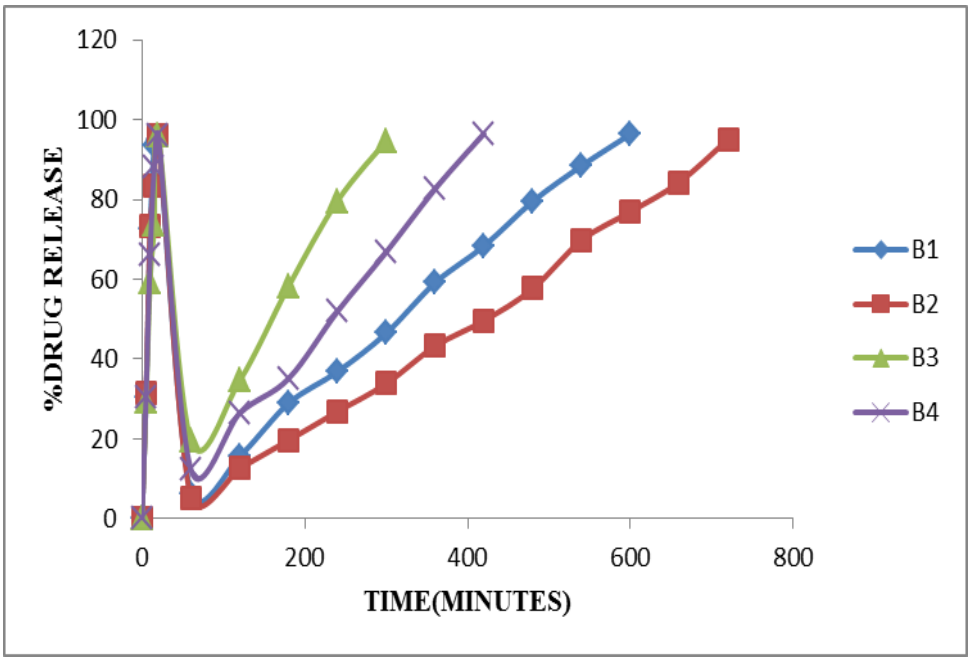


Fig 7.5 : Dissolution data of Pinodolol Floating bilayer tablets (B1-B4) by using synthetic polymers (Carbopol 934, Carbopol 940)

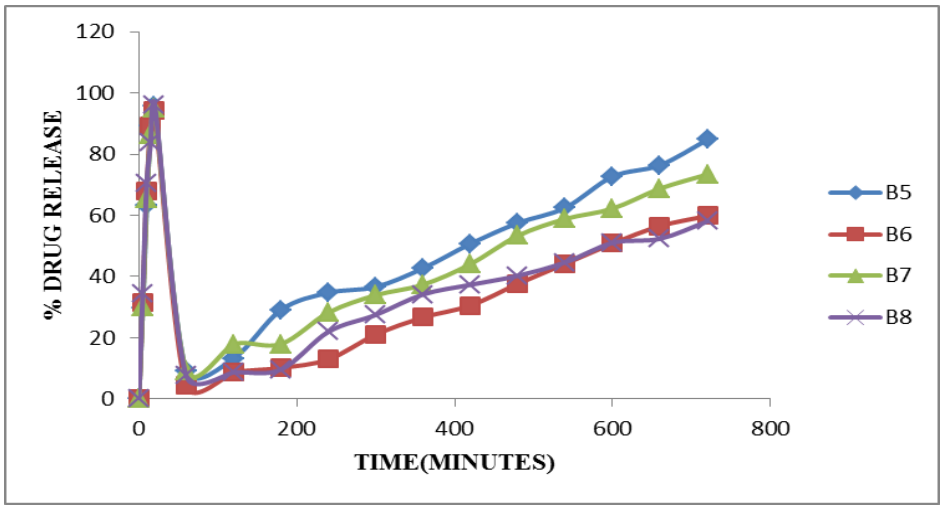


Fig 7.5 : Dissolution data of Pinodolol Floating bilayer tablets (B5-B8) by using Synthetic polymers (Eudragit L 100, Eudragit S100)

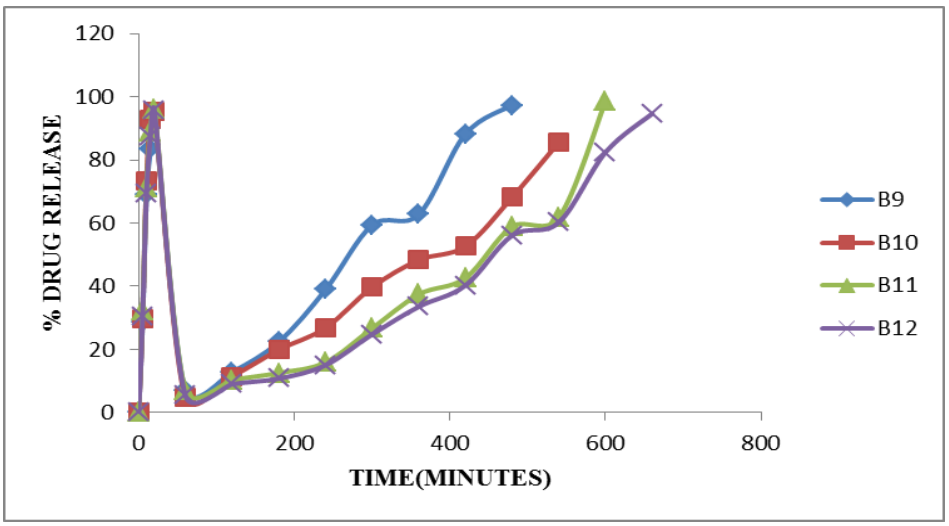


Fig 5 Dissolution data of Pinodolol Floating bilayer tablets (B9-B12) by using Synthetic polymers (HPMC K 15M, HPMC K100M)

Table 6 Dissolution data of Pinodolol Floating bilayer by using Natural polymers

Time (Min)	B13	B14	B15	B16	B17	B18	B19	B20
0	0	0	0	0	0	0	0	0
5	28.24	30.29	29.57	31.45	27.61	28.22	32.54	33.78
10	70.21	75.23	67.35	69.83	62.48	63.52	65.69	72.58
15	83.38	86.99	75.53	78.34	86.55	90.02	82.58	82.13
20	91.37	92.04	94.68	98.92	97.35	92.71	91.17	99.01
60(1 hr)	5.13	5.56	29.32	9.56	10.10	3.53	11.42	8.97
120(2 hr)	17.37	13.79	31.79	27.77	12.13	7.75	19.26	12.88
180 (3 hr)	28.94	29.89	46.55	39.82	25.16	12.89	29.33	19.87

240 (4 hr)	36.24	39.44	64.78	52.24	34.7	22.97	35.72	25.05
300 (5 hr)	41.32	43.96	73.44	67.54	39.97	37.14	38.56	29.88
360 (6 hr)	49.35	53.55	86.28	98.11	46.02	39.88	47.45	31.28
420 (7 hr)	56.49	59.73	97.09		51.55	40.95	49.19	34.02
480 (8 hr)	69.52	69.98			63.49	49.66	52.14	40.08
540 (9 hr)	72.89	76.28			71.62	54.07	59.97	45.78
600 (10 hr)	93.89	86.13			75.78	59.92	63.33	52.99
660 (11 hr)		91.44			76.39	60.5	79.96	54.57
720 (12 hr)		94.89			80.63	73.13	**97.88**	68.35

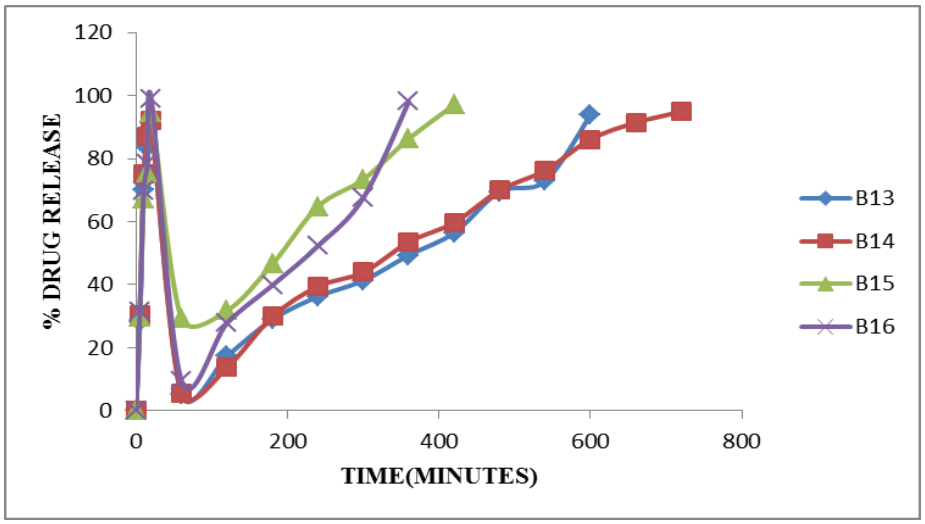


Fig 7.5 : Dissolution data of Pinodolol Floating bilayer tablets (B13-B16) by using Natural Polymers (Xanthan Gum, Guar Gum)

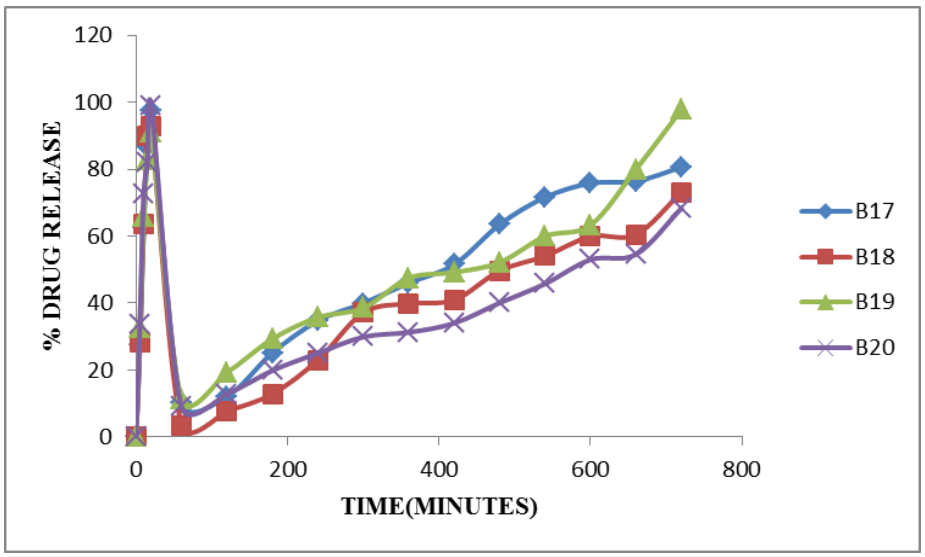


Fig 7.5 : Dissolution data of Pinodolol Floating bilayer tablets (B13-B16) by using Natural Polymers (Sodium Alginate, Caragennan)

Floating bilayer tablets of Pindolol formulations B1- B12 were developed by using Synthetic Polymers. B13- B20 Formulations were developed by using Natural Polymers. Floating Bilayer tablets containg 2 Layers i.e., Immediate Layer, Sustained Layer. From the Dissolution Data of Immediate Layer of Pindolol, the IR4 Formulation was showed highest drug release (96.58%) in 20 minutes. IR4 formulation was taken very less time to take the drug release when compared to other Immediate Layer Formulations.

IR4 formulation of Immediate layer, Sustained layer formulations blends (S1-S20) were compressed into single tablet individually. So B1- B20 formulations were the Pindolol Bilayer tablets.

The B1-B12 formulations were prepared by using Synthetic Polymers. B2 formulation was shown good drug release (**95.10%)** in 12 hours. it was containing 15 mg of carbopol 940 which is sufficient to control the drug release.

The B13-B20 formulations were prepared by using Natural Polymers. In that B19 formulation was shown best drug release (**97.88%)** within 12 hours. Finally Concluded that B19 formulation was optimised formulation.

Table no 3:Application of Release Rate Kinetics to Dissolution Data for best formulations (B2, B19):

KINETICS	**B2**	**B19**
	SR2 LAYER	**SR19 LAYER**
Zero order	R^2 =0.995	**R^2 = 0.9581**
First order	R^2 =0.819	R^2 = 0.873
Kars mayer peppas	**R^2 =0.998**	R^2 = 0.9362
Higuchi	R^2 =0.890	R^2 = 0.8936

Best formulation SR2, SR19 Layers were kept for release kinetic studies. SR2 Layer was following Kars mayer peppas release kinetics, SR19 was following Zero order release kinetics.

SR2 RELEASE KINETICS:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
5.12	1	#REF!	0.709	#REF!	1.977	#REF!	0.1953	-1.291	94.88	4.642	4.561	0.081
12.63	2	1.000	1.101	0.000	1.941	12.630	0.0792	-0.899	87.37	4.642	4.437	0.204
19.66	3	1.414	1.294	0.301	1.905	9.830	0.0509	-0.706	80.34	4.642	4.315	0.327
26.84	4	1.732	1.429	0.477	1.864	8.947	0.0373	-0.571	73.16	4.642	4.182	0.459
33.86	5	2.000	1.530	0.602	1.820	8.465	0.0295	-0.470	66.14	4.642	4.044	0.597
43.25	6	2.236	1.636	0.699	1.754	8.650	0.0231	-0.364	56.75	4.642	3.843	0.799
49.63	7	2.449	1.696	0.778	1.702	8.272	0.0201	-0.304	50.37	4.642	3.693	0.948
57.65	8	2.646	1.761	0.845	1.627	8.236	0.0173	-0.239	42.35	4.642	3.486	1.156
69.8	9	2.828	1.844	0.903	1.480	8.725	0.0143	-0.156	30.2	4.642	3.114	1.527
76.94	10	3.000	1.886	0.954	1.363	8.549	0.0130	-0.114	23.06	4.642	2.846	1.795
84.33	11	3.162	1.926	1.000	1.195	8.433	0.0119	-0.074	15.67	4.642	2.502	2.139
95.1	12	3.317	1.978	1.041	0.690	8.645	0.0105	-0.022	4.9	4.642	1.698	2.943

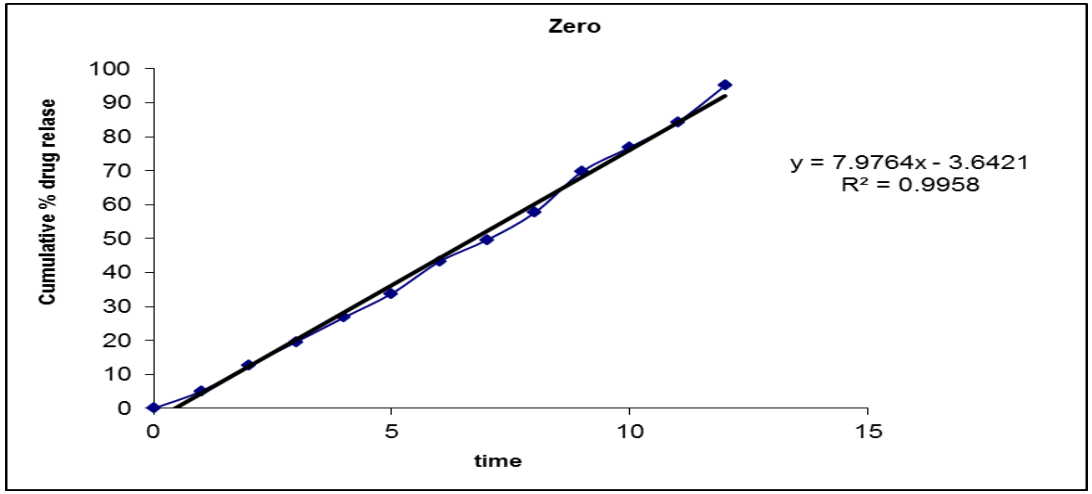


Figure: SR2 Formulation Zero Order Release Kinetics

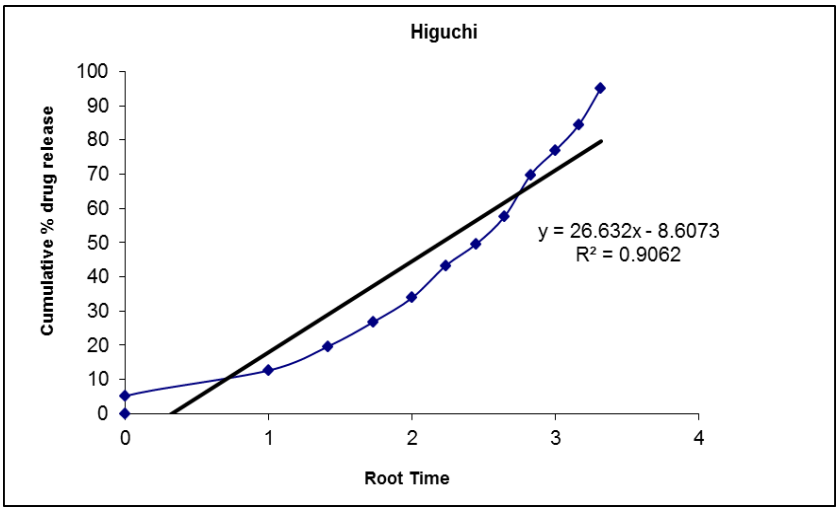


Figure: SR2 Formulation Higuchi graph

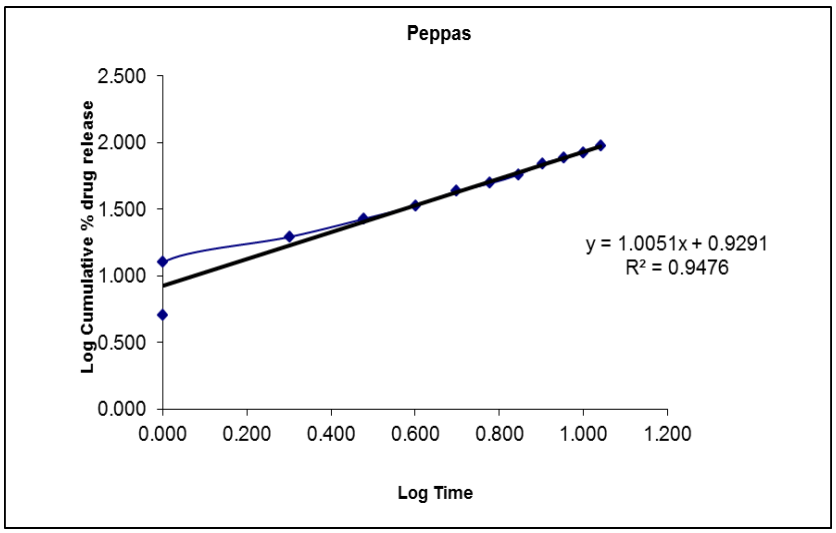


Figure: SR2 Formulation Peppas graph

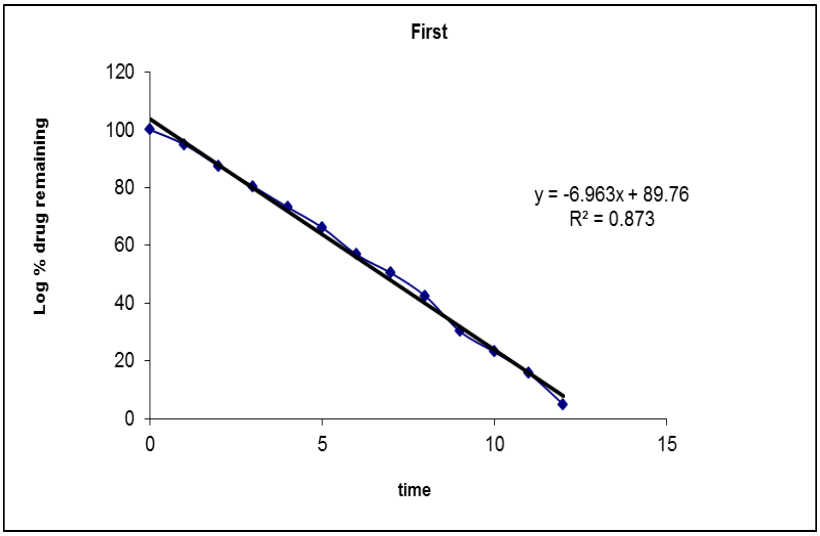


Figure: SR2 Formulation First order graph

SR19 RELEASE KINETICS

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
11.42	1	#REF!	1.058	#REF!	1.947	#REF!	0.0876	-0.942	88.58	4.642	4.458	0.184
19.26	2	1.000	1.285	0.000	1.907	19.260	0.0519	-0.715	80.74	4.642	4.322	0.319
29.33	3	1.414	1.467	0.301	1.849	14.665	0.0341	-0.533	70.67	4.642	4.134	0.507
35.72	4	1.732	1.553	0.477	1.808	11.907	0.0280	-0.447	64.28	4.642	4.006	0.636
38.56	5	2.000	1.586	0.602	1.788	9.640	0.0259	-0.414	61.44	4.642	3.946	0.696
47.45	6	2.236	1.676	0.699	1.721	9.490	0.0211	-0.324	52.55	4.642	3.746	0.896
49.19	7	2.449	1.692	0.778	1.706	8.198	0.0203	-0.308	50.81	4.642	3.704	0.938
52.14	8	2.646	1.717	0.845	1.680	7.449	0.0192	-0.283	47.86	4.642	3.631	1.011
59.97	9	2.828	1.778	0.903	1.602	7.496	0.0167	-0.222	40.03	4.642	3.421	1.221
63.33	10	3.000	1.802	0.954	1.564	7.037	0.0158	-0.198	36.67	4.642	3.322	1.319
79.96	11	3.162	1.903	1.000	1.302	7.996	0.0125	-0.097	20.04	4.642	2.716	1.925
97.88	12	3.317	1.991	1.041	0.326	8.898	0.0102	-0.009	2.12	4.642	1.285	3.357

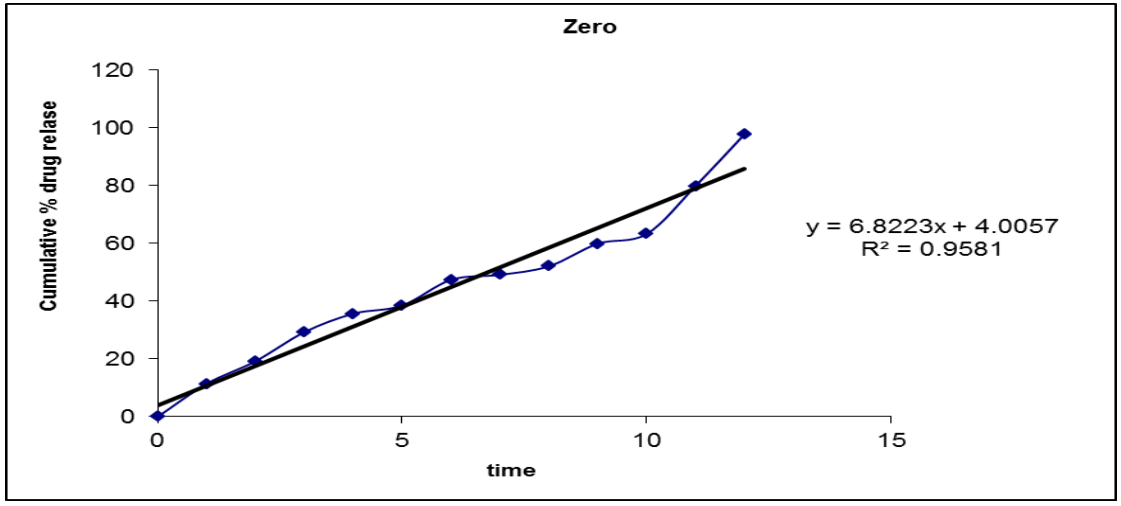


Figure: SR19 Formulation Zero Order Release Kinetics

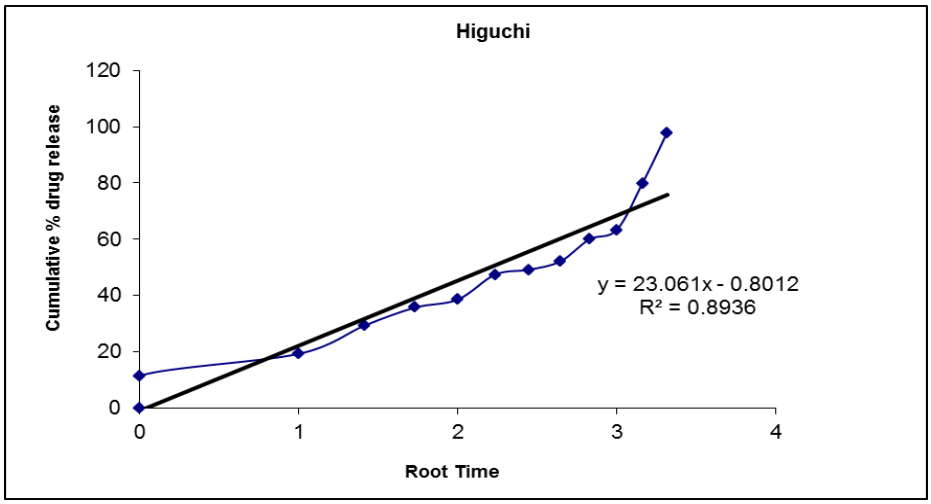


Figure: SR19 Formulation Higuchi graph

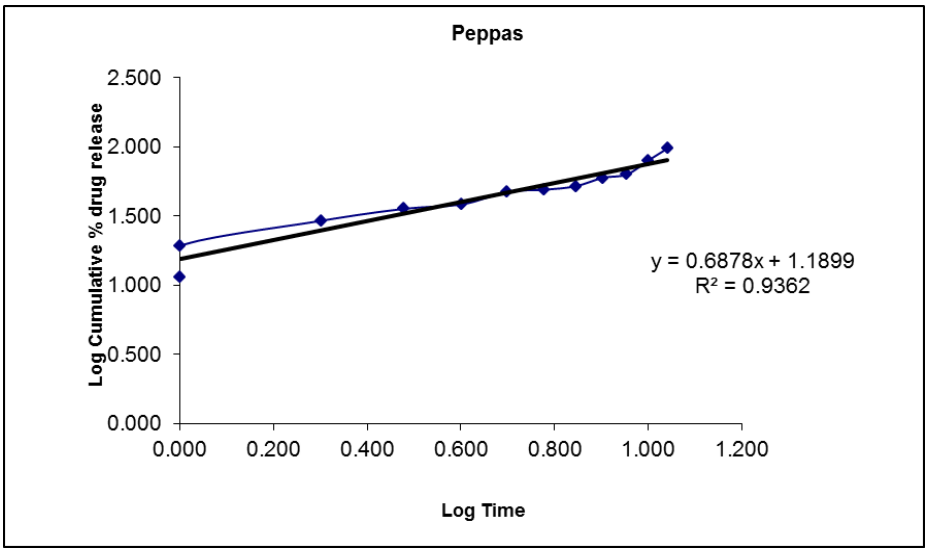


Figure: SR19 Formulation Peppas graph

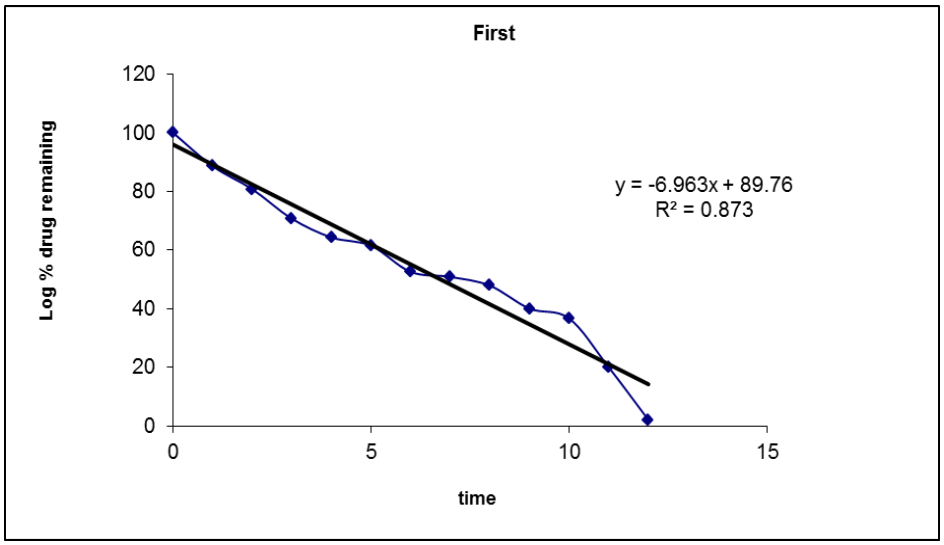


Figure: SR19 Formulation First order graph

B19 Formulation is considered as optimised formulation which follows zero order release kinetics.

CONCLUSION

The present study was carried out for Floating bilayer tablets of Pindolol. Immediate layers were prepared by direct compression method and Sustained layers were prepared by wet granulation method by considering the optimisation of sodium bicarbonate.

Immediate release Tablet powder blends were subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.49 to 0.56 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.68 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.48 to 0.59 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54 to 0.66 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Sustained Release layers were prepared using various polymers. Sodium bicarbonate was used as Gas generating agent. 15mg concentration of sodium bicarbonate was optimised and that concentration was used for all formulations. All the SR layer blends were performed for various pre and post compression studies. Those were found to be within limits.

From the dissolution data of Pinodolol Immediate release Layer, IR4 formulation was shown maximum drug release at 20min. i.e., 96.58%. Hence IR4 was concluded as optimised formulation for IR layer. Floating bilayer tablets of Pindolol formulations B1- B12 were developed by using Synthetic Polymers. B13- B20 Formulations were developed by using

Natural Polymers. Floating Bilayer tablets containg 2 Layers i.e., Immediate Layer, Sustained Layer. From the Dissolution Data of Immediate Layer of Pindolol, the IR4 Formulation was showed highest drug release (96.58%) in 20 minutes. IR4 formulation was taken very less time to take the drug release when compared to other Immediate Layer Formulations.

IR4 formulation of Immediate layer, Sustained layer formulations blends (S1-S20) were compressed into single tablet individually. So B1- B20 formulations were the Pindolol Bilayer tablets.

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The B13-B20 formulations were prepared by using Natural Polymers. In that B19 formulation was shown best drug release **(97.88%)** within 12 hours. Finally Concluded that B19 formulation was optimised formulation.

Best formulation SR2, SR19 Layers were kept for release kinetic studies. SR2 Layer was following Kars mayer peppas release kinetics, SR19 was following Zero order release kinetics.

B19 Formulation is considered as optimised formulation because more drug release which follows zero order release kinetics.

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