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FORMULATION AND EVALUATION OF ATENOLOL ANTIHYPERTENSIVE BILAYER TABLET

Dr. G. Mariyappan* and L. Varsha

Department of Pharmaceutics, Pallavan Pharmacy College, Kolivakkam, Iyyengarkulam, Kanchipuram-631502.

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***Corresponding Author**
Dr. G. Mariyappan
Department of Pharmaceutics, Pallavan Pharmacy College, Kolivakkam, Iyyengarkulam, Kanchipuram-631502.

ABSTARCT

The present investigation was focused on formulation and evaluation of Atenolol bilayer tablet which is used as antihypertensive agent. Bilayer tablet consist of two layer namely immediate release and sustained release. The Eight formulation of bilayer tablets were prepared by using different concentration of polymer. Immediate release layer was formulated by direct compression using polymers such as cross carmellose sodium, sodium starch glycolate. Meanwhile, sustain release was formulated by wet granulation using HPMC K15, chitosan and guar gum. Preparations of tablet were carried out by keeping the tablets weight as constant (350mg±20mg). And then characterization of prepared tablet was done by evaluation of hardness, friability, weight variation, drug content and in-vitro release of formulation (F1-F8). The precompression parameters of all formulation were studied like angle of repose, flow property, bulk density, tapped density, Carr's index, Hausner's ratio. The post compression parameters such as appearance, weight variation, uniformity of content of all formula were within the acceptable limits. The best formulations F8 was selected based on the thickness (3.41±0.01), hardness (6.3±0.17), friability (0.30±0.02), average weight (129,251), weight variation (1.5%) and drug content (99.16). The best formulation of Atenolol shows drug release was found to be F8 (89.95%). The in-vitro drug release kinetics showed that the formulation were compiles first order kinetics as correlation coefficient (r^2)(0.934-0.985).

KEYWORDS: Bilayer tablet, sodium starch glycolate, HPMC K15, In-vitro dissolution release.

INTRODUCTION

Controlled release dosage form is a term accustomed to describe the dosage forms having drug release features supported on the time, course and/or location and which are designed to accomplish therapeutic or convenience objectives which don't seem to be offered by conventional release dosage forms. However, it is intended to disintegrate rapidly and The design of a bilayer tablet dosage form holds many advantages over conventional dosage forms like reduction in frequency of drug administration, improved patient compliance, reduction exhibits instant drug release. It is also related to fluctuations in drug plasma levels, which causes reduction or loss in drug effectiveness or increased incidence of side-effects. Therefore, to compensate the dip in drug plasma concentration as a result of metabolism and excretion, it is necessary to administer the dosage form several times per day. On the premises of these consideration, the bilayer tablets are developed to produce two different release rates or biphasic release of a drug from a one dosage form in which one layer is formulated to get immediate release effect of the drug, with the aim of reaching a high plasma concentration in a very short period of time while second layer is intended as sustained release layer, which provides effective plasma concentration by a maintenance dose of drug for an extended period of time. in drug fluctuation in blood and quantitative reduction in total drug usage when compared with conventional therapy. Atenolol belongs to antihypertensive drug. It is freely soluble in water and soluble in alcohols (ethanol). It is odorless white powder with melting point of 152-154℃. It competes with sympathomimetic neurotransmitters like catecholamine for binding at beta (1)-adrenergic receptors with in the heart and vascular smooth muscle, inhibiting sympathetic stimulation. This results in a depletion in resting heart rate, systolic and diastolic blood pressure, cardiac output and reflex postural hypotension. Higher doses of atenolol also competitively block beta (2)-adrenergic responses with in the bronchial and vascular smooth muscles.

Absorption-Atenolol is well absorbed from GIT and its bioavailability is 40% by first pass metabolism. Peak plasma concentrations of 300-800ng/ml are seen at between 2-4 hours after administration of a100mg dose. The effect of atenolol on pulse rate usually begins at one hour, peaks at 2-4 hours and persists for twenty-four hours. Distribution-Atenolol distributes into most tissues expect for brain and CSF. Approximately 5-15% binds to plasma protein. Elimination-Atenolol is eliminated through renal excretion of unchanged medicine. The plasma half- life is 6-7 hours in patients with normal renal function16-27 hours in patients with creatinine clearances of 15-35ml/minute/1.73m^2 and will exceed 27 hours as renal

impairment progresses. For the preparation of biphasic release with variable concentrations of superdisintegrant in immediate release layer and rate retarding polymer in sustained release layer for adjusting release pattern consistent with the requirement of therapy and IP guidelines of atenolol sustained release tablet.

MATERIALS AND METHODS

Materials

Table No 1: List of materials used in the Experiments.

SL.NO.	MATERIALS	USE	SUPPLIER
1.	Aten	API	Yarrow chem products, Mumbai.
2.	Maize Starch	Diluent	Yarrow chem products, Mumbai.
3.	HPMC K15	Excipient	Yarrow chem products, Mumbai.
4.	Mannitol	Vehicle	Yarrow chem products, Mumbai.
5.	Spray Dried Lactose	Excipient	Yarrow chem products, Mumbai.
6.	Crospovidone	Superdisintegrant	Yarrow chem products, Mumbai.
7.	Magnesium Stearate	Lubricant	Yarrow chem products, Mumbai.
8.	Talc	Glidant	Yarrow chem products, Mumbai.

Table No 2: List of equipment used in the Experimentation.

SL.NO	NAME OF THE INSTRUMENT	MODEL/COMPANY NAME
1.	Electronic Analytical Balance	Shimadzu AUX-224
2.	UV Visible Sectrophotometer	UV-1700, Shimadzu corporation, Japan
3.	FTIR	Alpha Brucker
4.	Oven	Remi Instruments Private Limited, Mumbai.
5 .	Stability Chamber	Thermo lab
6.	Multi Station Tablet Press	Lab press, CIP machineries pvt. Ltd. Ahmedabad
7.	Vernier calipers	Electrolab, Serve well instrument pvt. Ltd Bangalore
8.	Monsanto hardness tester	Electrolab, Serve well instrument pvt, ltd. Bangalore
9.	Friabilator	Electrolab, Serve well instrument pvt.ltd.Bangalore
10.	USP Dissolution testing apparatus type-I(Basket type)	Electrolab, Serve well instrument pvt.ltd.Bangalore
11.	Disintegration test apparatus(USP)	Electrolab, Serve well instrument pvt.ltds.Bangalore
12.	Freeze Dryer	Labconco,U.S.A

PREFORMULATION

Pre formulation may be described as investigational research and development where the studies or the experiment characterizes the physical, chemical, mechanical properties of a new drug molecule/substance, in order to develop, safe and effective dosage form. Pre-

formulation investigation enables us the understanding or knowledge of the deficiencies molecule weakness, decay mechanism or drug decomposition occurring during the formulation process and those can be eradicated and to fulfill the goal of designing optimum drug delivery systems.

MORPHOLOGY: The drug was identified morphologically by visual bases.

ANALYTICAL METHOD

PREPARATION OF STANDARD CALIBRATION CURVE OF ATENOLOL IN METHANOL: Atenolol was estimated by UV visible spectroscopy. Spectrophotometric estimation of atenolol was carried out in methanol. Stock solution was prepared 1000µ/ml and determined spectrophotometric estimation of atenolol with 275nm as maximum absorbance. The study was carried out in triplicates.

PREPARATION OF STOCK SOLUTION (1mg/1ml): 100mg of pure Atenolol was accurately weighed and transferred into 100ml volumetric standard flask and added methanol to dissolve the drug and made up to 100ml methanol.

PREPARATION OF STANDARD GRAPH: According to Beer's law, the graph was drawn by measuring the absorbance of various concentration of drug solution against the blank from stock solution(1mg/ml) of various concentrations 0.05ml,0.1ml,0.15ml,0.2ml and 0.25&3ml were pipette out and transferred into 10ml of volumetric flask and make up with phosphate buffer. The drug concentration in each flask was 5µ/ml, 10µ/ml, 15µ/ml, 20µ/ml and 25µ/ml, 30µ/ml respectively. Absorbance of each solution was observed at 275nm in an UV-visible spectrometer and the calibration graph was drawn by the concentration against absorbance.

MELTING POINT OF ATENOLOL- LIST OF EQUIPMENT

- Mel temp II apparatus with special thermometer
- Sample
- Vial of capillary tube (closed on one end)
- Watch glass with capillary tube
- Spatula
- Test tube.

PROCEDURE

- Transfer a few crystals to the watch glass.
- Grind the crystals to a powder using the end of the tube.
- Press open end of tube into powder collect the amount.
- Invert the tube and tap it sharply on bench to pack the crystals into closed.
- Put the filled capillary tube into the Mel Tem II apparatus.
- Repeat this process up to three times.
- The melting point of pure Atenolol is found to be 158℃-160

DOSE CALCULATION

Dt = Dn+Ds

=Dn(1+Kt)

=Dn{1+(0.693/t1/2×time)}

=25{1+(0.693/7×5)}

=25(1.97) [t1/2=7 hours, Time=8, Actual dose =50mg]

=49.5 mg (Adjusted dose to make 50mg Tablets)

INCOMPATIBILITY STUDIES: Drug-excipient compatibility studies by FT-IR: Excipients are integral components of almost all pharmaceutical dosage forms. To investigate any possible interaction between the drug and the utilized excipients, IR spectrum of pure drug (Atenolol) and its physical mixture with excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. Infrared spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug and to compare the sample with for its initial and differential storage condition for month up to expiry.

GRANULATION METHOD FOR ATENOLOL BILAYER TABLETS

IMMEDIATE RELEASE: Direct compression method: 25mg of the drug and the excipients were passed through sieve#60, lubricants were added by geometrical dilution followed by through mixing for 20min.The prepared mass was compressed by using 10 mm concave faced punches in a controlled environment to get the average weight of 125 mg tablets – formulations were prepared by using different concentrations of disintegrants. The compressed formulations were shown in the following table.

GRANULATION METHOD FOR SUSTAINED RELEASE FORMULATION

WET GRANULATION TECHNIQUE: Weigh all the ingredient in required quantity. Transfer all ingredients into mortar triturate for 10 min. Until we get final powder and sieve the material with sieve no.60. Then transfer the material into blender for proper distribution of drug in blend for 10 min. Then add sufficient amount of starch paste to obtain the granules. Lubrication: The granules were compressed using 12 station rotary tableting machine equipped with concave type, round punches of 10 min diameter. After the lubrication granules were compressed using 12 station rotary tableting machine equipped with Concave type, round punches of 10 min diameter.

TABLET COMPRESSION: The prepared granules of both layers were compressed on single rotary compression machine on 10 mm concave shaped round punch. First immediate release granules were fill into die cavity and it is compressed with lower pressure and after that in the same die cavity another granules (sustained release) granules were filled and the final compression was done only after both the granules occupied on the basis of color in immediate release granule.

FORMULATIONS OF ATENOLOL BILAYER TABLETS

Batch size; 100 tablets

Weight of each tablet; 360 mg

Table No 3: Immediate Release Tablet Formulation Formulae.

INGREDIENTS/FORMULATIONS	IAT 1	IAT 2	IAT 3	IAT 4	IAT 5	IAT 6	IAT 7	IAT 8
Atenolol	25	25	25	25	25	25	25	25
Cros carmellose sodium	25	45	30	25	45	30	25	30
Sodium starch glycolate	25	40	30	25	40	30	25	10
Lactose	25	25	20	25	25	20	25	25
Starch 1500	10	10	10	25	10	10	10	10
Microcrystalline cellulose	15	20	20	10	20	20	20	15
Magnesium stearate	5	5	5	15	5	5	5	5
Talc	3	3	3	5	3	3	3	3

Table No 4: Sustained Release Tablet Formulation Formulae.

INGREDIENTS/FORMULATIONS	SA T1	SA T2	SA T3	SA T4	SA T5	SA T6	SA T7	SA T8
Atenolol	25	25	25	25	25	25	25	25
Xanthum Gum	15	25	15					
Guar Gum	15	15	25					25
Carboxy Methyl Cellulose	15	15	25					
HPMC K15	0			15	25	40	25	50
Chitosan				15	25	25	40	25
Sodium Bi Carbonate	15	15	15	15	15	15	15	15
Maize Starch	25	25	25	25	25	25	25	25
Magnesium Stearate	10	10	10	10	10	10	10	10
Talc	3	3	3	3	3	3	3	3

Evaluation parameters: Pre compression parameters for Bilayer tablets containing immediate and sustained release layers of Atenolol.

(a) Bulk density: The prepared blend was poured into a graduated cylinder. The weight of powder (M) and bulk volume (V_b) was determined. The bulk density was calculated using the formula.

$$\rho b = \frac{M}{Vb}$$

(b) Tapped density: A known mass of blend was transferred to measuring cylinder and tapped for a fixed time. The weight (M) of the blend and minimum volume (V_b) occupied in cylinder was measured. The tapped density (ρ_t) was calculated using the formula.

$$\text{TBD} = \frac{\text{Weight of the powder blend}}{\text{Tapped volume of the packing}}$$

(c) Compressibility index: Compressibility is determined by calculating the flow of powder. It was an indication of the ease with which a material can be induced to flow is given by compressibility index(I) which is calculated as follows

$$C_1 = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} \times 100$$

Where, ρ_t = Tapped density, ρ_b=Bulk density

Table No 5: Compressibility index as an indication of powder flow properties.

Carr's index (%)	Type of flow
>12	Excellent
12.0-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

(d) Hausner ratio: It is calculated by the following formula

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Where Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25)

(e) Angle of repose: Angle of repose was estimated by funnel method. The funnel was placed vertically until definite cone height (h) was obtained, after which the blend was poured through the funnel. Radius of the heap(r) was measured and angle of repose(θ) was calculated using the formula.

Tan θ=h/r

Therefore; $\theta=\tan^{-1}$

Where, θ is Angle of repose; h is height of cone; r is radius of cone.

Table No 6: Angle of repose as an indication of powder flow properties.

Angle of Repose(˚)	Type of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

POST COMPRESSION PARAMETERS

Physical appearance: The tablets were inspected for smoothness, absence of cracks, chips and other undesirable characteristics. If tablets were coloured, they were evaluated for mottling and other evidence of non-uniform colour distribution except where they are used intentionally.

Thickness: Thickness is important criteria for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

Weight Variation Test: 20 tablets were picked randomly from each batch and weighed individually on electronic balance. The individual weight of tablet was correlated with average weight for the weight variations. The following percentage deviation in weight variation is allowed. The results are shown in table.

Table No 7: Percentage deviation in weight variation Limits.

Average weight	% Difference
130 mg	Less than 10
130-324 mg	Less than 7.5
324 mg	Less than 5

Bilayer fracture: In this test, one layer of the tablet was fixed inside an ad-hoc adjusted cavity, while the outer layer was exposed to the blade. The outer layer of the bilayer tablet was then pushed by the blade. Hence, a curve force (registered on the blade) versus displacement (of the blade itself) was recorded. The maximum value of the curve corresponds to the breaking point: the layers are completely separated at this point. Then, resistance applied was haulted and the force recorded drops rapidly to zero.

Friability: Tablet strength was tested by using EF-2 Friabilator.20 tablets were weighed and placed in the EF-2 friabilator (USP) and operated for 100 revolutions (25 rpm for 4min), taken out and dedusted. By reweighing the tablets, percentage weight loss was calculated. The % friability was then calculated by,

$$F = \frac{(\text{Winitial}) - (\text{Wfinal})}{(\text{Winitial})} \times 100$$

Disintegration time: Disintegration time is the time required for a tablet to break up into granules of definite size (or smaller), under proper test conditions. The disintegration test is performed in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm length and 2.15 mm in diameter the bottom of which consists of a10 mesh sieve. The basket is raised and lowered 28-32 times per minute in the medium of 900ml which is maintained at 37±2℃. Six tablets were placed in each of the tubes and the time required for complete movement of tablet fragments through the sieve (#10) was considered as the disintegration time of the tablet.

Drug Content: Drug content from each batch (IAT1+SAT1 to IAT8+SAT8) was determined by powdering the pre-weighed sample of at least 10 tablets in glass mortar and pestle. By using standard curve, Atenolol content of tablets was calculated. Each batch evaluated in triplicate (n=3) for estimation of drug content.

In-Vitro Dissolution Studies: Dissolution studies were performed for all the formulation combinations in triplicate, in vitro drug release was studied by using USP 36 type II apparatus, i.e., Rotating paddle(Disso TDT 08 L, Electro lab). The dissolution was performed

in 900ml acidic buffer pH 1.2. The temperature was maintained at 37±0.5° and the speed of paddle was kept 50 rpm during dissolution study. Samples of 5ml was collected at the interval of one hour and replaced with 5ml buffer solution so as to maintained sink condition during study. The absorbance of samples was deducted on UV spectrophotometer at 225 nm.

Kinetic Release Study: To analyze the mechanism of the drug release rate kinetics of the dosage form, the values obtained were plotted as:

A) Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation=$K.t_{1/2}$, Where, F is the amount of drug released, K is the release rate constant, and t is the release time. The graph was plotted for cumulative drug released versus square root of time, a straight line was obtained which indicates the drug was released by diffusion mechanism. The slope is equal to, K.

B) Korsmeyer and peppas release model: The release rate data were fitted to the following equation**,** $\mathbf{M_t/M_\infty = K.t^n}$ Where, M_t/M_∞ is the fraction of drug release, K is the release constant, t is the drug release time, and n is the diffusion exponent which is dependent on the shape of the matrix dosage forms. When the data is plotted as Log of drug released versus Log time, yields as straight-line with a slope equal to n and the K can be obtained from Y-intercept.

C) Zero order release rate kinetics: To study the zero –order release kinetics the release rate data are fitted to the following equation. **F= K.t** , Where F represents the fraction of drug release, k illustrates the release rate constant and t depicts the release time. The graph was plotted for cumulative percentage drug release versus time, if the obtained plot was linear then the data obeys Zero-order kinetics, with a slope equal to K_0[49.]

D) First order kinetics: ln (1-F) =-K_1 t(4). Where F depicts the fraction of drug released in time t and K_1 belongs to first order.

RESULT

1. Morphological study

a) Colour: A small quantity of Atenolol powder was taken in butter paper and viewed in well- illuminated place.

b) Taste and odour: Very less quantity of Atenolol was used to get taste with the help of tongue which was also smelled to get the odour.

Table No 8: Organoleptic properties for Atenolol.

Test	Specification/limits	Observations
Colour	White	White
Taste	Bitter	Bitter
Odour	Odourless	Odourless

Table No 9: Standard calibration curve for Atenolol in 0.1 HCl.

Concentration (µ gm /ml)	Absorbance (mean±Sd)
0	0
5	0.47±0.005
10	0.93±0.003
15	0.143±0.003
20	0.187±0.005
25	0.235±0.005
30	0.280±0.005

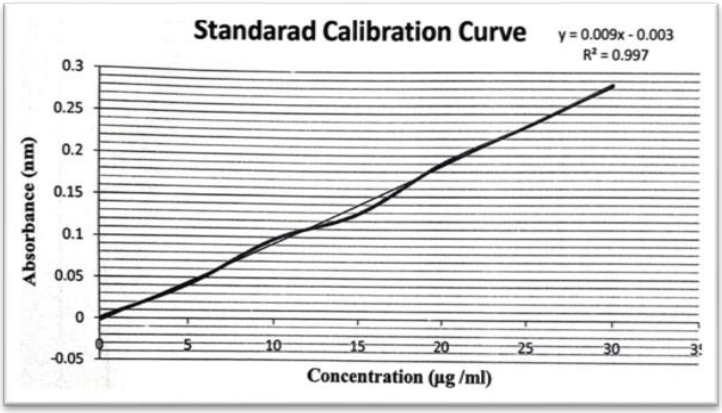

Fig. 1: Standard calibration curve of atenolol in 0.1 N HCl.

Compatibility studies by IR Studies

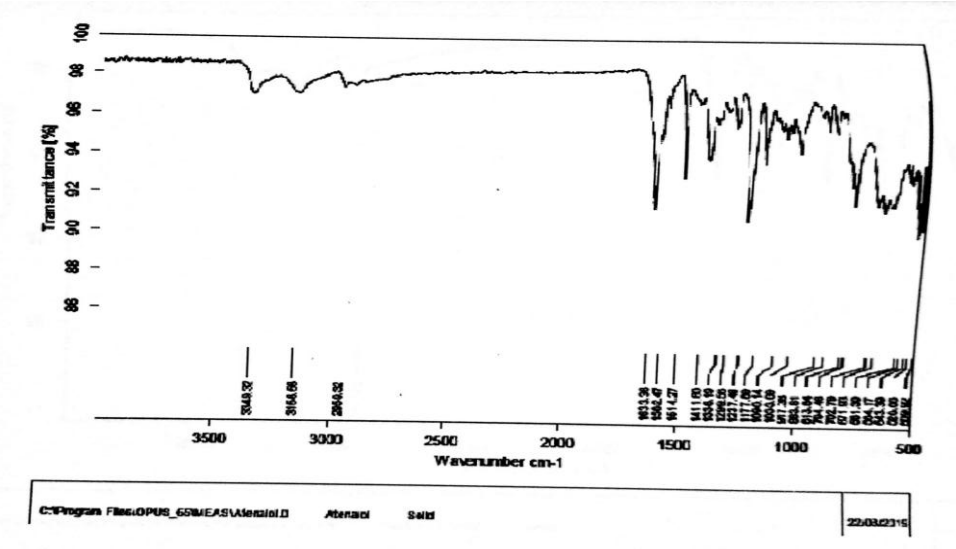

Fig. 2: FT-IR spectra of pure Atenolol.

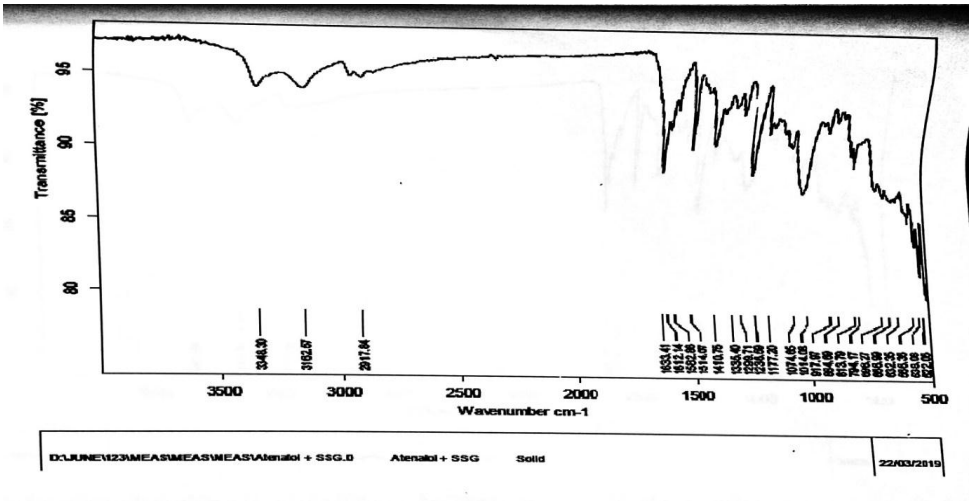

Fig. 3: FT-IR spectra of Atenolol + SSG.

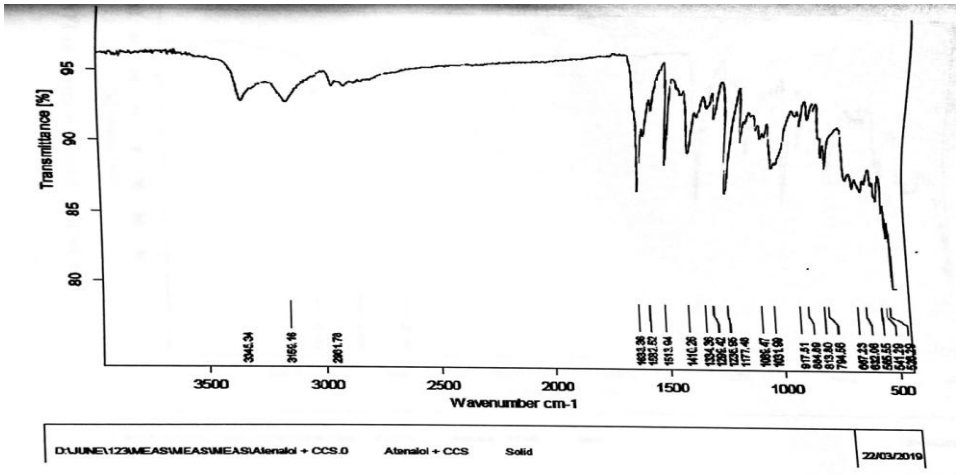

Fig-4: FT-IR spectra of Atenolol + Cros carmellose sodium.

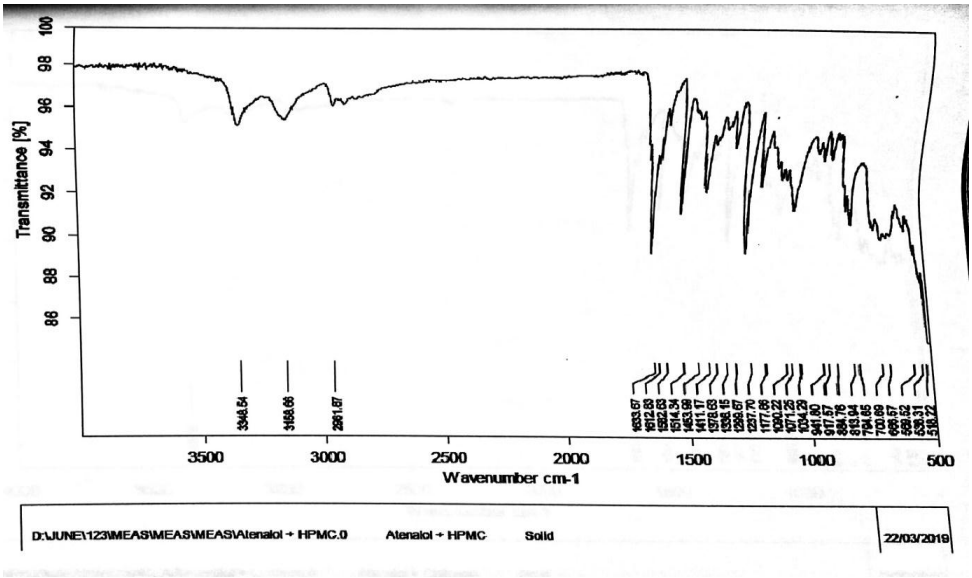

Fig -5: FT-IR spectra of Atenolol + HPMC K15.

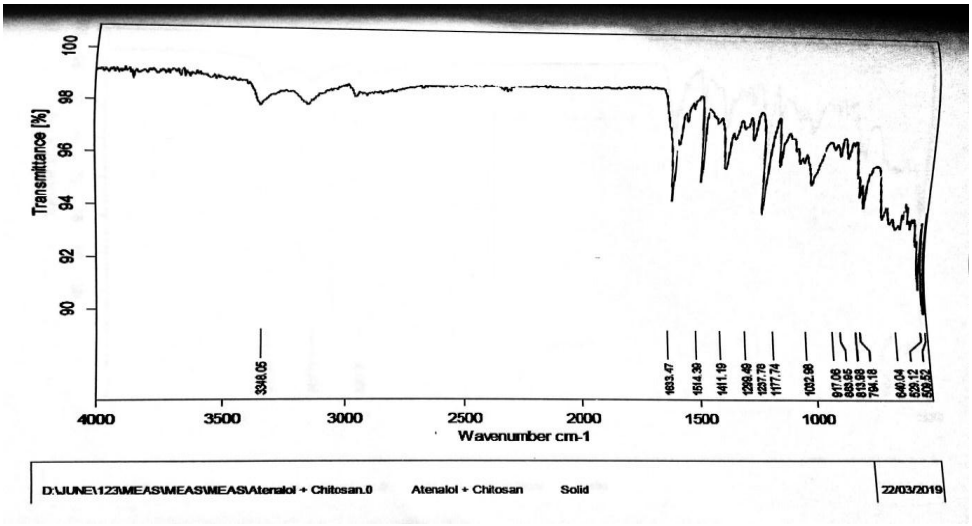

Fig-6: FT-IR spectra of Atenolol + Chitosan.

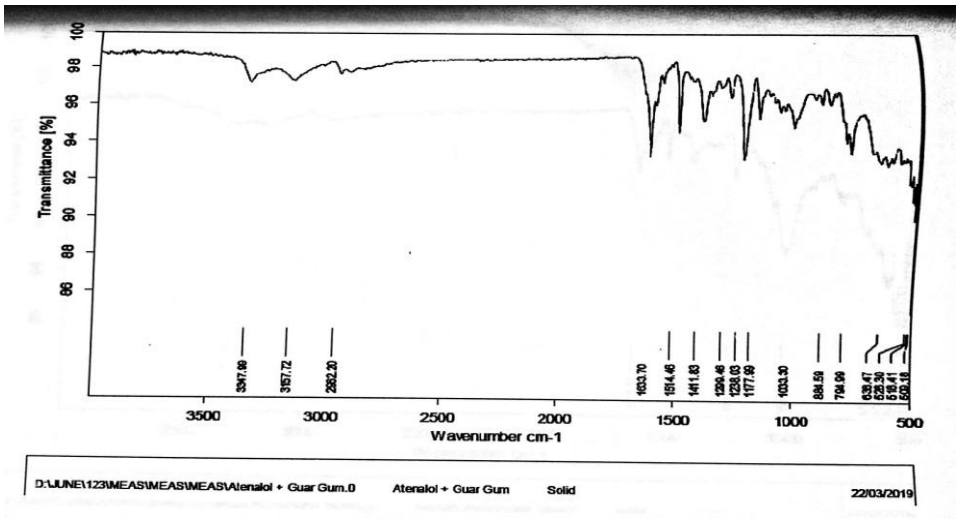

Fig-7: FT-IR spectra of Atenolol + Guar Gum.

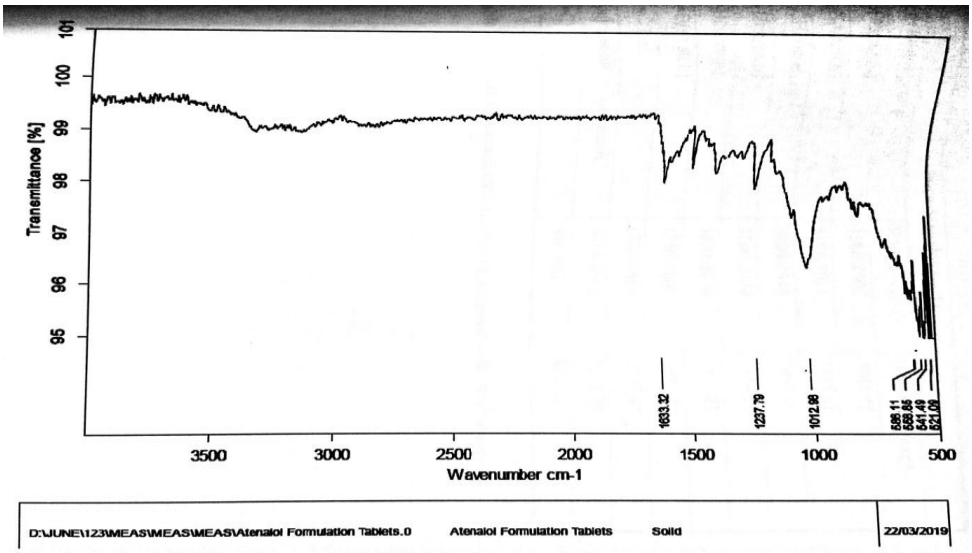

Fig-8: FT-IR spectra of optimized formula.

Pure Atenolol (cm^{-1})

Table No 10: IR Compatibility studies of Atenolol with Excipients.

Functional group	Range	Observed range
-OH(stretch)	3368-2500	3345.97
H-N(stretch)	3198-3071	3155.61
C-CH3(stretch)	3000-2966	2957.11
CH2(stretch)	3100-2924	2914.11
C-H(stretch)	3000-2870	2847.01
C=O(stretch)	1760-1666	1693.79
O=C-NH2	1760-1665	1632.87
Conjugated C=C(aromatic)	1614-1585	1611.28
C=CH2	900-886	884.11

Table No 11: Interpretation of IR of pure drug, polymers and execipients.

STANDARD VALUE OF DRUG(CM^{-1})	DRUG +SSG	DRUG +CCS	DRUG+ CHITOSAN	DRUG+HPMC K15	DRUG+ GUAR GUM
3345.97	3348.30	3345.34	3348.05	3348.54	3347.99
3155.61	3162.57	3159.16	-	3158.66	3157.72
2957.11	-	2961.78	-	2961.87	2962.20
2914.11	2917.84	-	-	-	
2847.01	-	-	2847.71	-	
1693.79	-	-	-	-	
1632.87	1633.41	1633.36	1633.47	1633.67	1633.70
1611.28	1612.14	-	-	1612.83	-
884.11	884.69	884.89	883.95	884.76	884.59

Pre-compression parameters of optimization series.

Table no 12: Pre-compression parameters for Atenolol Immediate Release layer.

Batch code	Bulkdensity (gm/cm^3)	Tappeddensity (gm/cm^3)	Carr's Index(I_C)	Hausner ratio (H_R)	Angle of repose(θ)
IAT1(mg)	0.50	0.58	14.5	1.14	31.21
IAT2(mg)	0.49	0.56	13.7	1.15	30.23
IAT3(mg)	0.48	0.53	11.5	1.13	29.76
IAT4(mg)	0.49	0.53	11.3	1.14	29.53
IAT5(mg)	0.49	0.56	13.2	1.16	28.42
IAT6(mg)	0.5	0.58	14.79	1.15	29.78
IAT7(mg)	0.47	0.54	15.36	1.18	30.11
IAT8(mg)	0.45	0.57	16.09	1.17	28.29

Table no 13:Pre-compression parameters for Atenolol sustained release.

Batch code	Bulk density (gm/cm^3)	Tappeddensity (gm/cm^3)	Carr's index(I_C)	Hausner ratio(H_R)	Angle of repose(θ)
SAT1	0.455±0.29	0.5918±0.19	21.5±0.13	1.24±0.16	30.1±0.28
SAT2	0.468±0.32	0.594±0.27	23±0.17	1.26±0.17	29.3±0.25
SAT3	0.457±0.39	0.577±0.32	21.4±0.23	1.23±0.14	29.3±0.23

SAT4	0.455±0.25	0.54±0.19	20.8±0.31	1.26±0.14	29.2±0.23
SAT5	0.454±0.27	0.573±0.39	18.7±0.33	1.24±0.12	27.4±0.35
SAT6	0.454±0.31	0.552±0.15	18.8±0.41	1.26±0.16	27.2±0.25
SAT7	0.454±0.42	0.556±0.27	15.6±0.28	1.19±0.13	26.1±0.55
SAT8	0.468±0.4	0.585±0.3	19.9±0.09	1.22±0.19	29.2±0.43

Post compression parameter for formulations

Table no 14: Post compression study for IR and SR layer tablets of Atenolol.

SL.NO	TESTS	SPECIFICATION	IAT1+ SAT1	IAT2+ SAT2	IAT3+ SAT3	IAT4+ SAT4
1.	Thickness(mm)	3.42-3.98 mm	3.47±0.05	3.40±0.01	3.50±0.05	3.50±0.05
2.	Hardness(kg/ cm^3)	5.0-6.0 kg/cm^2	6.2±0.25	6.1±0.10	6.3±0.35	6.1±0.35
3.	Friability (%)	Not more than 1%	0.35±0.04	0.33±0.02	0.29±0.04	0.29±0.04
4.	Average weight(mg)	125-135 mg[IR]	128	130	128	129
		250 mg [SR]	249	251	250	251
5.	Weight variation	±7.5% from the average weight	2.0%	1.2%	2.1%	1.65%

Table no 15: Post compression study for IR and SR layer tablets of Atenolol.

SL. NO	TESTS	SPECIFICATION	IAT5+ SAT5	IAT6+ SAT6	IAT7+ SAT7	IAT8+ SAT8
1.	Thickness(mm)	3.42-3.98 mm	3.60±0.05	3.41±0.01	3.49±0.05	3.41±0.01
2.	Hardness(kg/cm^2)	5.0-8.0 kg/cm^2	6.3±0.02	6.2±0.17	6.5±0.15	6.3±0.17
3.	Friability (%)	Not more than 1%	0.35±0.04	0.30±0.02	0.25±0.04	0.30±0.02
4.	Average weight(mg)	125-135 mg[IR]	128	130	128	129
		250 mg[SR]	249	251	250	251
5.	Weight variation	±7.5% from the average weight	2.0%	1.2%	2.1%	1.5%

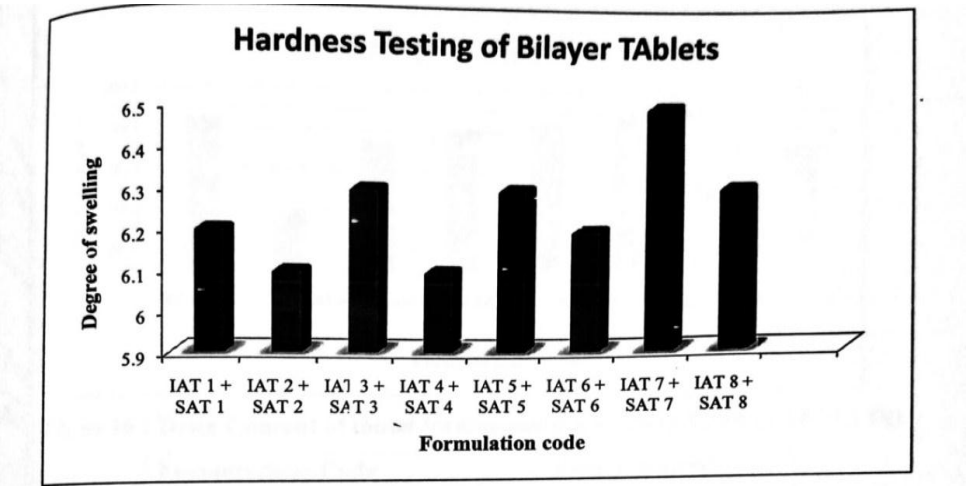

Fig- 9: Comparison of hardness of Atenolol bilayer tablets formulations.

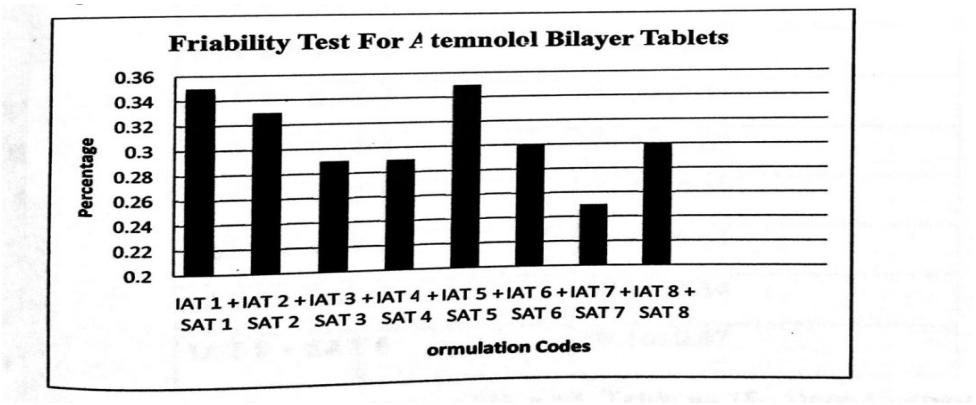

Fig-10: Comparison of friability of Atenolol bilayer tablets formulations.

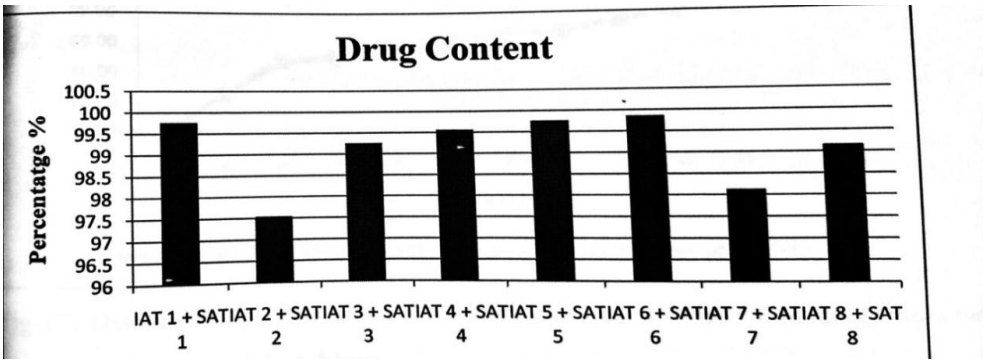

Fig- 11: Drug content of tablet formulations (IAT1+SAT1 to IAT8 + SAT8).

Table no 15: Drug content of tablet formulations (IAT1+SAT1 to IAT8+SAT8).

Formulations code	% Drug content*
IAT1+SAT1	99.76±0.62
IAT2+SAT2	97.54±0.76
IAT3+SAT3	99.26±0.47
IAT4+SAT4	99.56±0.60
IAT5+SAT5	99.76±0.33
IAT6+SAT6	99.86±0.33
IAT7+SAT7	98.13±0.34
IAT8+SAT8	99.16±0.47

Where,* All values are mean ± SD, n=3.

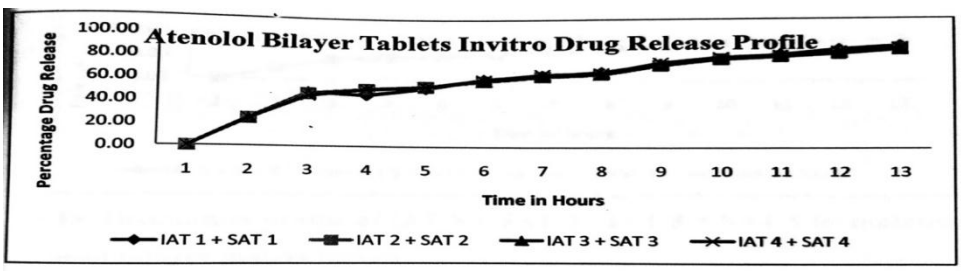

Fig 12: Dissolution profile of IAT1+SAT1 –IAT4+SAT4 formulations of Atenolol bilayer matrix tablets.

Table no 16: Dissolution profile of IAT1+SAT1 –IAT4+SAT4 formulations of Atenolol bilayer matrix tablets.

TIME (hr)	%CDR			
	IAT1+SAT1	IAT2+SAT2	IAT3+SAT3	IAT4+SAT4
0	0.00	0.00	0.00	0.00
1	24.58	24.27	24.11	24.58
2	47.91	46.98	46.36	44.80
3	45.74	51.03	50.72	51.03
4	52.12	53.68	53.36	53.52
5	60.52	58.81	59.28	60.06
6	64.10	63.17	63.95	65.04
7	67.06	65.04	65.66	66.13
8	74.38	72.98	73.44	75.47
9	78.58	78.58	78.43	80.14
10	82.47	80.61	80.76	81.85
11	86.99	83.72	83.26	85.12
12	89.95	87.93	86.84	88.40

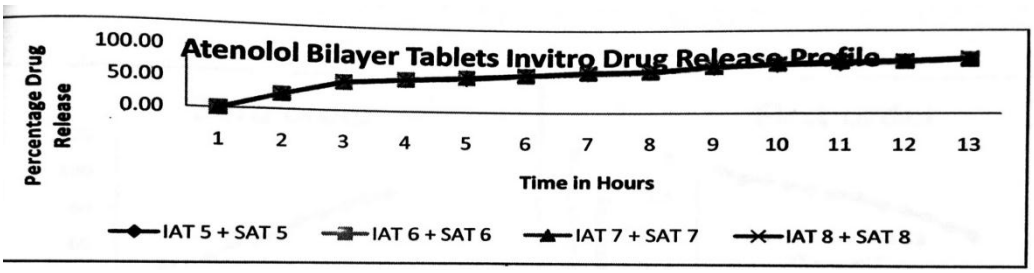

Fig 13: Dissolution profile of IAT5+SAT5-IAT8+SAT8 formulations of Atenolol bilayer matrix tablets.

Table no 17: Dissolution profile of IAT 5+SAT5 –IAT8+SAT8 formulations of Atenolol bilayer matrix tablets.

TIME (hr)	%CDR			
	IAT5+SAT5	IAT6+SAT6	IAT7+SAT7	IAT8+SAT8
0	0.00	0.00	0.00	0.00
1	24.42	24.73	24.58	24.58
2	45.27	45.89	46.05	46.83
3	51.50	52.58	52.12	52.27
4	55.08	56.79	57.25	57.25
5	60.37	60.99	61.30	61.92
6	64.57	65.50	66.59	66.28
7	66.60	67.22	68.15	68.15
8	74.84	76.09	76.71	76.87
9	79.05	80.60	81.23	80.92
10	81.08	83.88	84.50	84.19
11	83.72	84.50	85.75	85.59
12	87.31	87.93	88.40	89.95

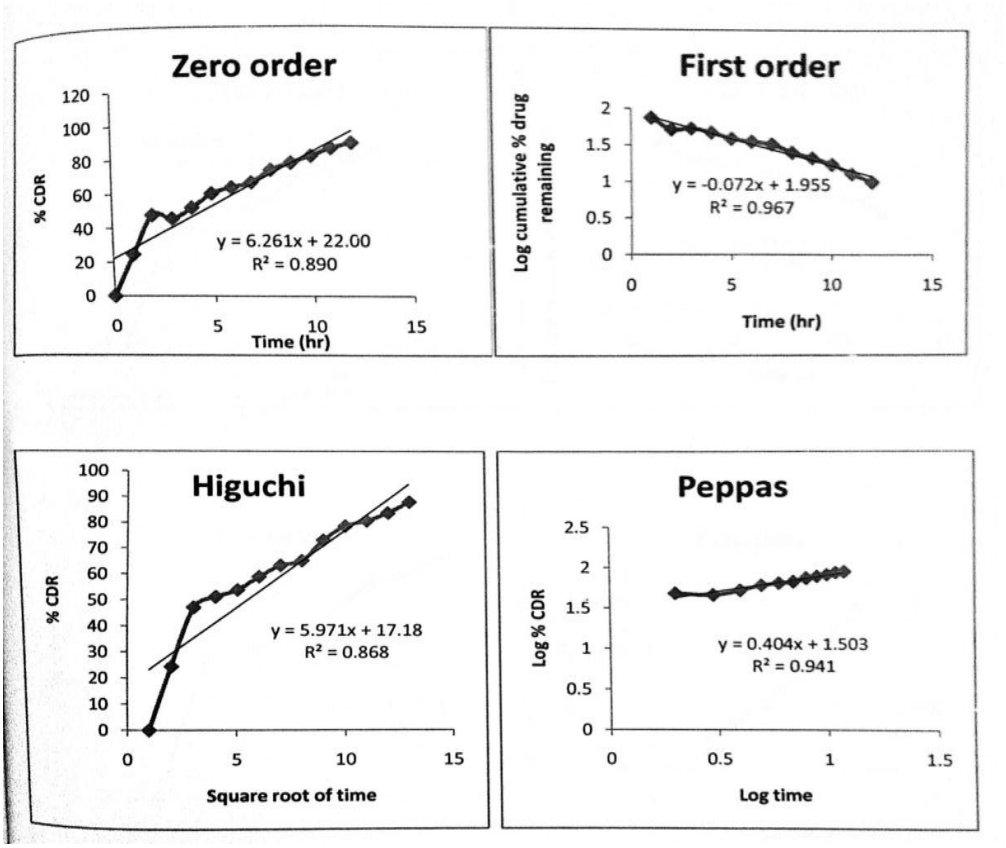

Fig 14: Dissolution kinetic profile of IAT1+SAT1 formulation of Atenolol bilayer tablets.

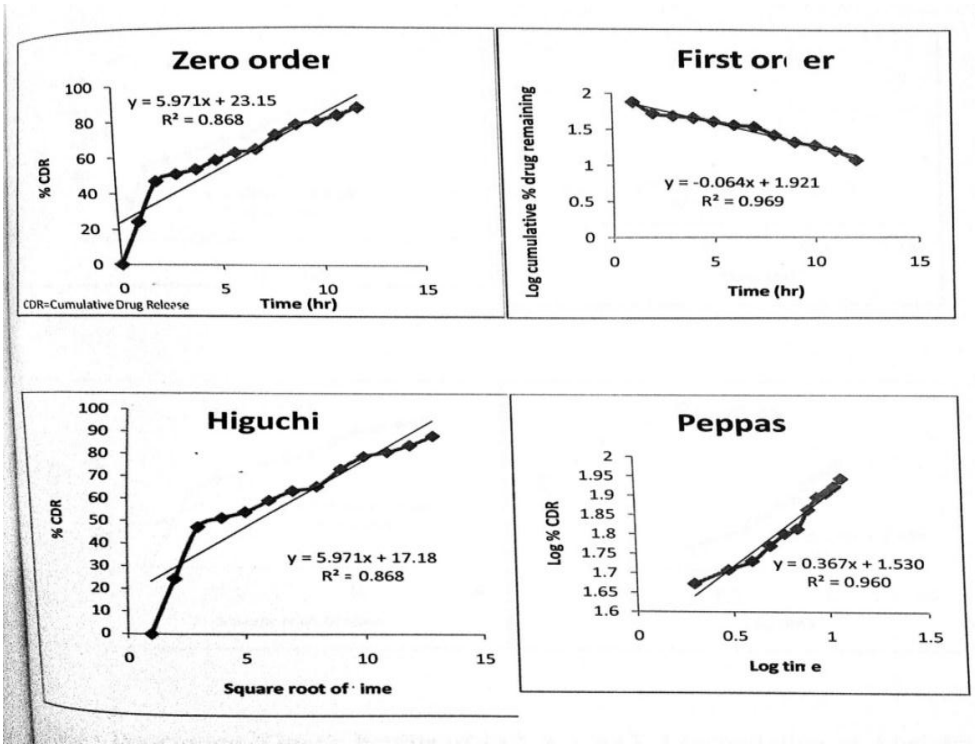

Fig 15: Dissolution kinetic profile of IAT2+SAT2 formulation of Atenolol bilayer tablets.

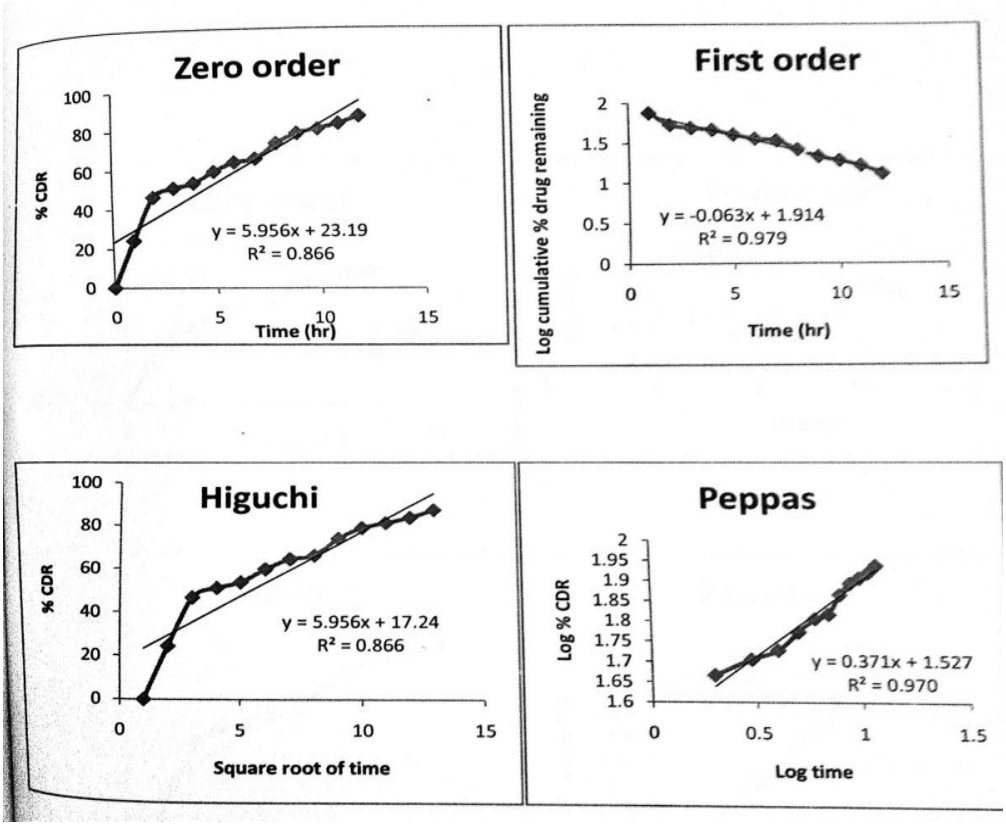

Fig 16: Dissolution kinetic profile of IAT3+SAT3 formulation of Atenolol bilayer tablets.

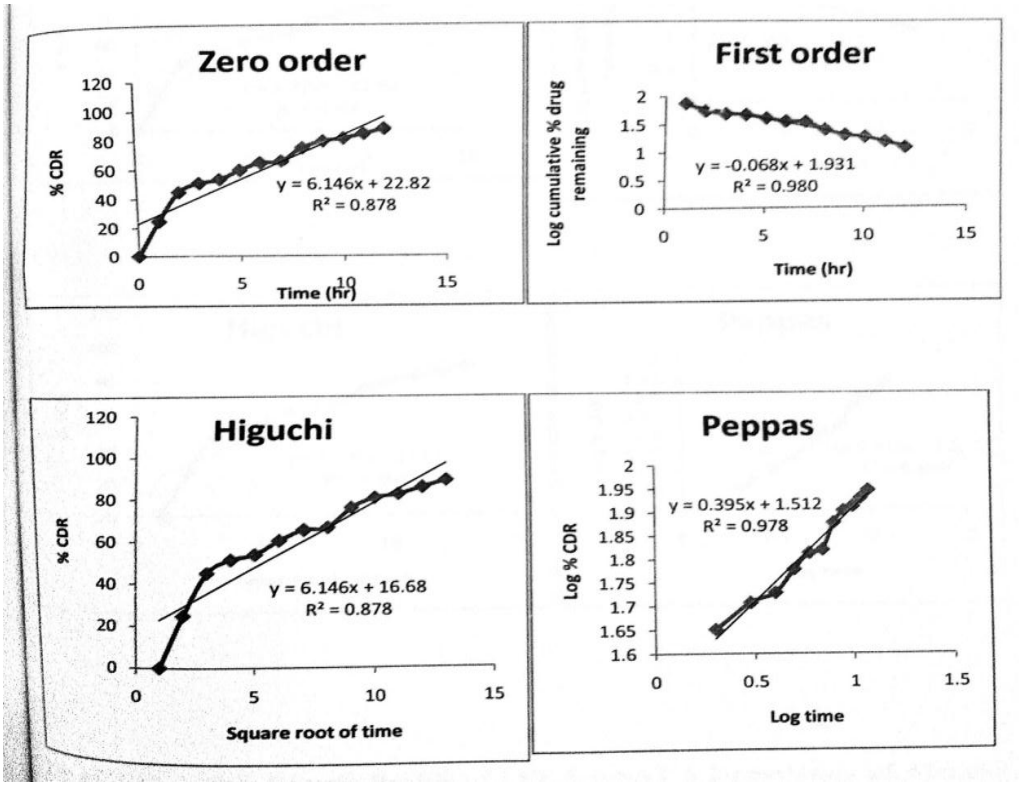

Fig 17: Dissolution kinetic profile of IAT4+SAT4formulation of Atenolol bilayer tablets.

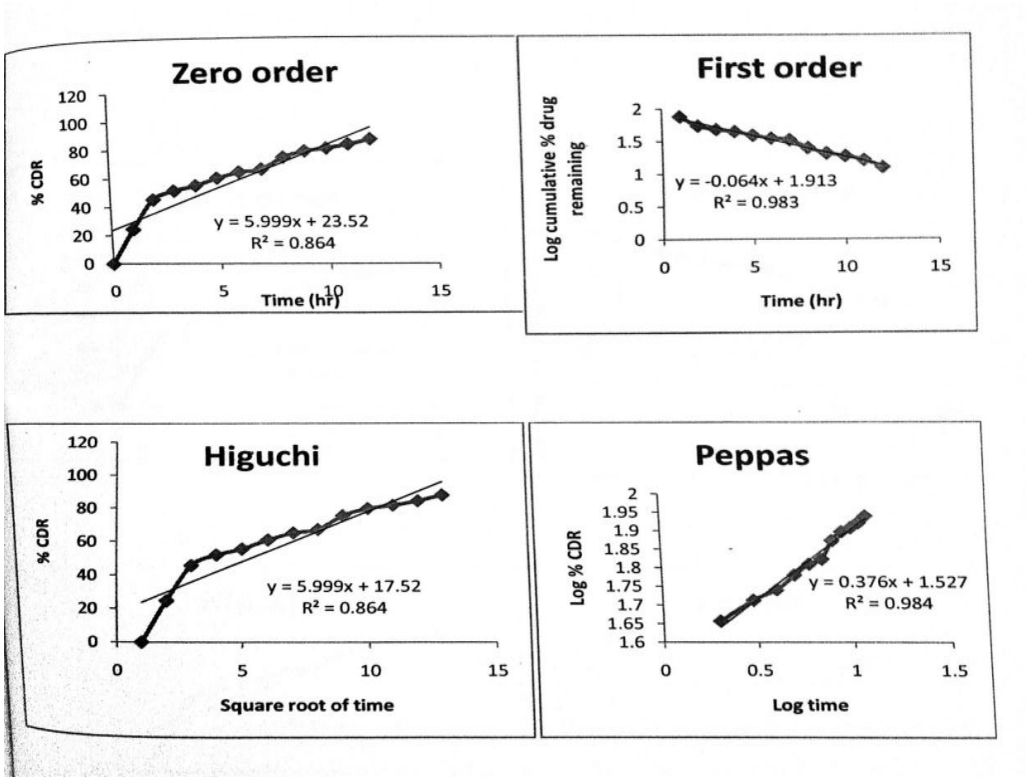

Fig. 18: Dissolution kinetic profile of IAT5+SAT5 formulation of Atenolol bilayer tablets.

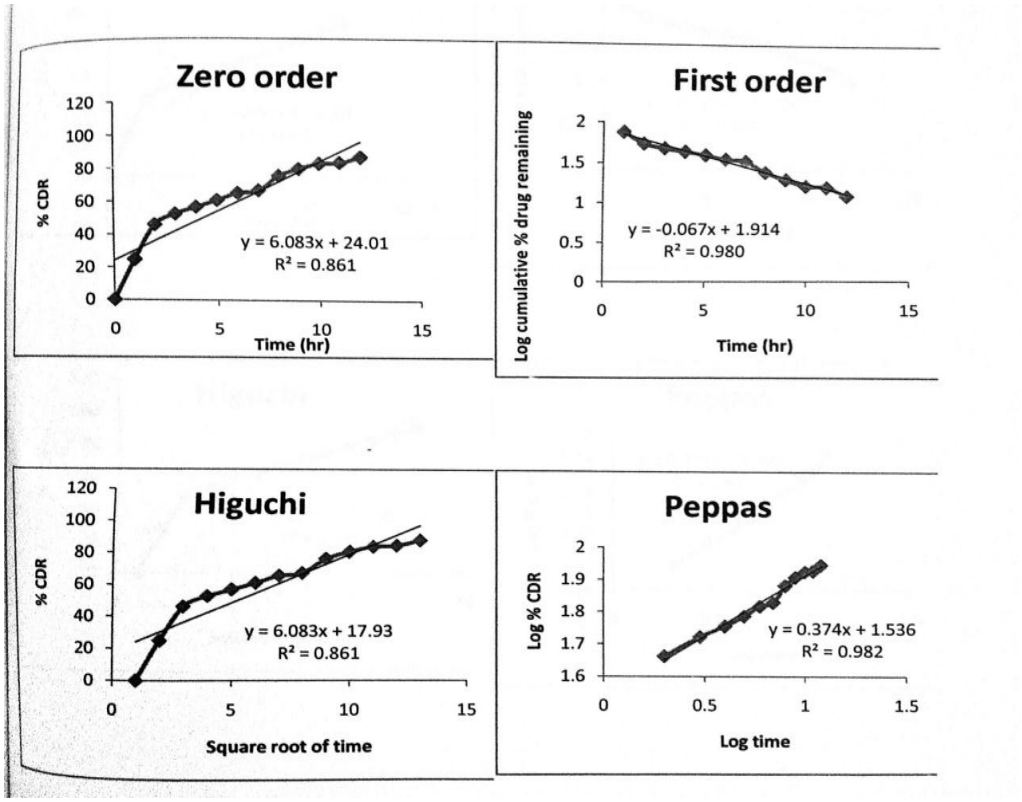

Fig. 19: Disolution kinetic profile of IAT6+SAT6 formulation of Atenolol bilayer tablets.

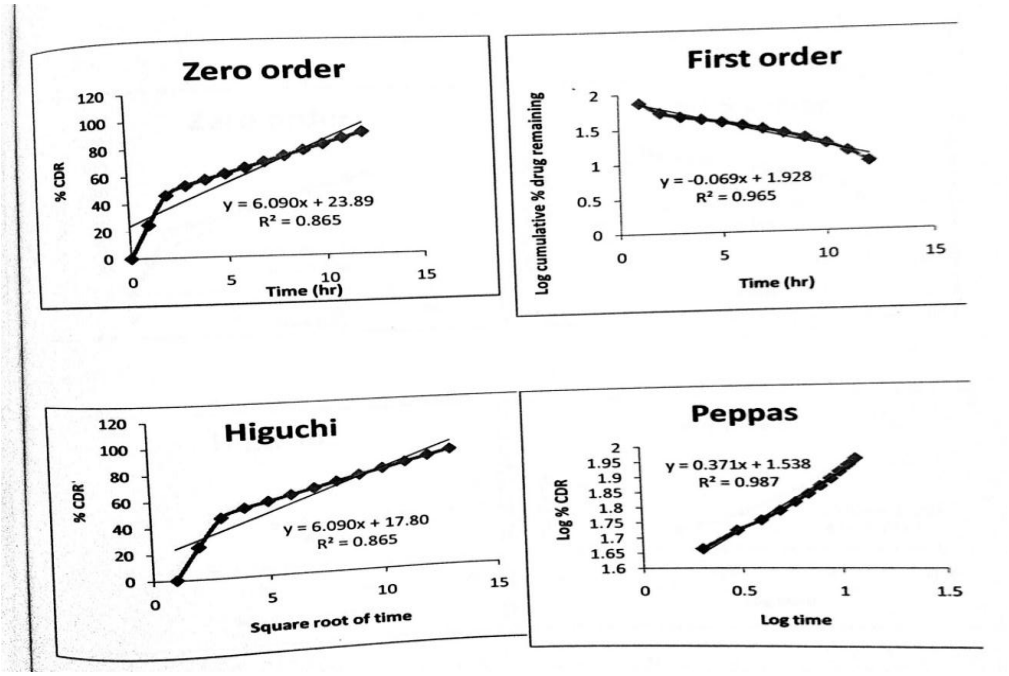

Fig. 20: Dissolution kinetic profile of IAT7+SAT7 formulation of Atenolol bilayertablets.

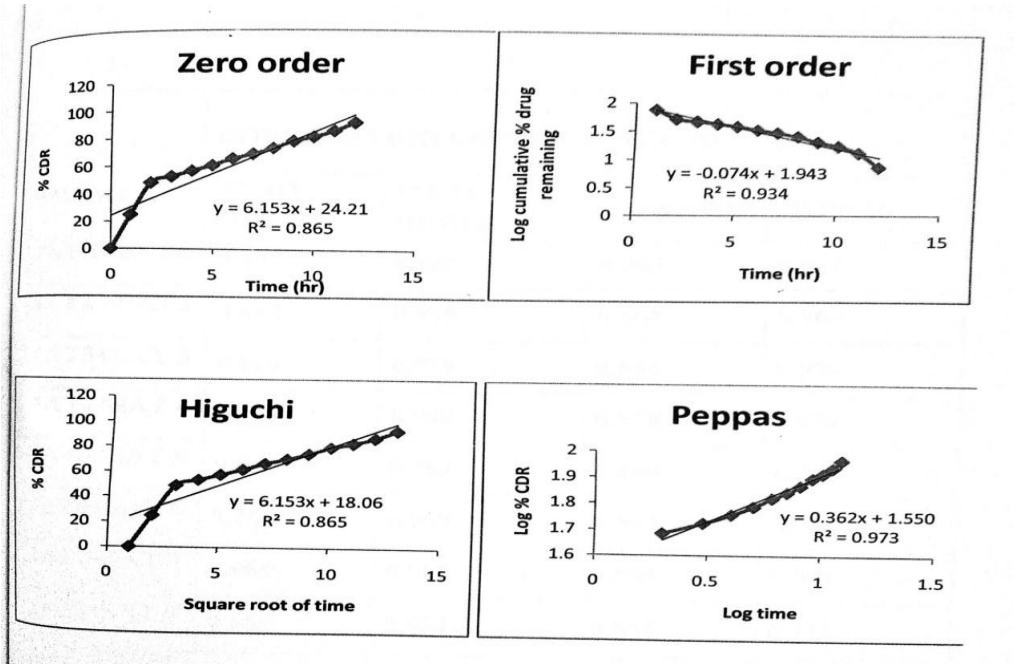

Fig. 21: Dissolution kinetic profile of IAT8+SAT8 formulation of Atenolol bilayer tablets.

Table No 18: Curve fitting data of the release rate profile of Atenolol bilayer tablets.

FORMULA	CORRELATION COEFFICIENTS(R)			
	ZERO ORDER	FIRST ORDER	HIGUCHI	PEPPAS
IAT1+SAT1	0.890	0.985	0.985	0.941

IAT2+SAT2	0.868	0.969	0.868	0.960
IAT3+SAT3	0.866	0.979	0.866	0.970
IAT4+SAT4	0.878	0.980	0.878	0.978
IAT5+SAT5	0.864	0.983	0.864	0.984
IAT6+SAT6	0.861	0.980	0.861	0.982
IAT7+SAT7	0.865	0.965	0.865	0.987
IAT8+SAT8	0.865	0.934	0.865	0.973

DISCUSSION

Atenolol bilayer tablets were formulated according to formulate by applying empirical development of formula for the robust formulation with Immediate and Sustained release formulations using different polymers. Immediate release layer is formulated by direct compression and sustained release layer is prepared by wet granulation technique. The Pre compression parameters and the post compression parameters and *In-vitro* dissolution studies were evaluated results of the parameters were discussed below.

Morphological study: All the characteristics of drug like colour, odour, taste are as per the IP 2014 and found suitably fit for the bilayer tablet formulation. Morphological studies were described in the Table No: 8.

Standard Calibration Curve of Atenolol: It was found that the estimation of Atenolol by UV Spectrophotometric method at 225 nm in 0.1N HCl had good reproducibility and this method was used in the study. For the standard curve the correlation curve was closer to 1 that is 0.997, at the concentration range, 5-30µg/ml. The regression equation generated was y=0.009x-0.003 R^2= 0.997.

Melting point determination: The melting point of the drug sample was found to be 154.6℃ which is within the reported range of 155̊-157℃. It complies with the standards thus indicating the purity of the drug sample and Atenolol can be used for Bilayer tablet preparation.

Fourier Transform Infrared Spectroscopy: According to ICH guidelines, FTIR Spectra of pure drug, polymer and their physical mixture were recorded. The drug, polymer and physical mixtures of drug and polymers were scanned for absorbance. The IR spectral graphs of Atenolol alone and with excipient combination graphs were shown in Fig.no 2-8. Standard frequencies of Atenolol were given table no 9 and 10. The spectra obtained from the physical mixtures showed all the principle peaks at or around the requisite wave numbers of pure

drugs with minor shift of the peaks. Hence it was confirmed that there was no interaction between Atenolol and polymers, the excipients.

Formulation of bilayer tablets: Eight formulations of bilayer tablets were prepared using polymers such as Cross carmellose Sodium, Sodium starch glycolate with lactose base for immediate release formulation and HPMC K15, Chitosan and guar gum as base for sustained release formulation in different concentrations and proportions by wet granulation technique in sustaining layer and sodium starch glycolate is used as superdisintegrant in immediate release later by direct compression. By keeping constant tablet weight as (350mg±20mg) all the formulation were prepared.

PRECOMPRESION STUDIES

Pre-compression parameters for Atenolol Immediate Release layer: The drug and the powder blends are evaluated for pre compression parameters. The results are given in the table no 11.The bulk density of the drug and IR blends without lubricant ranged from 0.45 to 0.50g/cm and tapped density ranged from 0.53 to 0.58g/cm. The compressibility index of the drug and IR blend ranged from 11.3 to 16.09% and Hausner's ratio ranged from 1.13 to 1.18. The angle of repose of IR blends ranged from 28.42 to 31.21 the formulated blends showed fair to good flow property.

Pre compression parameters for Atenolol sustained release layer: The drug and the powder blends are evaluated for pre compression parameters .The results are given in the table no 12. The bulk density of the drug and SR blends without lubricant ranged from 0.454 to 0.468g/cm and tapped density ranged from 0.54 to 0.594g/cm. The compressibility index of the drug and SR blend ranged from 15.6 to 23.0% and Hausner's ratio ranged from 1.19 to 1.23 .The angle of repose of SR blends ranged from 27.4 to 30.10 the formulated blends showed fair to good flow property.

POST COMPRESSION STUDY FOR IR AND SR LAYER TABLETS

Thickness: Thickness of formulation of IAT1+SAT1 to IAT8+SAT8 shown in table no: 13 and 14.Results were lies in the ranges of 3.40 to 3.60mm and it was found stable and reproducible. The tablet remained intact for the duration of the study, with no visible signs of tablet defects.

Hardness: The average hardness of all the compression coated tablet formulation of IAT1+SAT1 to IAT8+SAT8 lies in the range of 6.13 to 6.3kg/cm^2.

Friability: The average friability of all the formulation of IAT1+SAT1 to IAT8+SAT8 lies in the range of 0.25to0.35%.

Weight variation test: Weight variation of the bilayer tablets was shown table no: 13 and 14 and results were found to be in the variation around1.4 to2.45. Thus all the formulations were favourable with the standards given in IP.

Drug content: Drug content of the developed formulation was shown table no: 15 and Fig no: -11. Results were found to be near 99.16 to 99.86%, which is within the official requirements. The formulation prepared by using bilayer tablets drug content was ranging from 99.16 to 99.86% which proves uniform Atenolol distribution throughout the all formulations.

In-vitro release study: A hydrophilic and natural gum polymer controlled release system is a dynamic system composed of polymer-wetting, hydration and dissolution. At the same time, other soluble excipients or drug(s) will dissolve and diffuse from tablet while the insoluble ingredients will be held in place until the polymer swell and adhesive properties. Since the diffusional release of soluble drug such as Atenolol may primarily be controlled by the gel thickness (diffusion layer), the drug release was found to be decreased, by increasing the polymer level. On increasing the thickness of gel layer drug diffusion out of tablet was retarted.

The immediate release part of the powders were prepared by direct compression by using super disintegrants to detach the part of the tablet as we called as immediate release layer of tablet and other part of sustained release formulation part started to get swollen by the effect of bioadhesive polymers used in the formulation such as HPMC K15, Chitosan and Guar gum induces to hydrate with aiding the swelling and bind with wall of stomach there by it slowly allow atenolol drug diffuse through gel matrix of bio adhesive polymer complex. Dissolution studies of prepared bilayer matrix tablets were carried out in pH1.2 for 12 hours. The samples were analysed spectrophotometrically at225nm.

The dissolution rates of all bilayer tablets were studied by using USP type II apparatus (paddle type) in 0.1Hcl.The release of atenolol from bilayer tablets depends on the type and

concentration of polymer. The formulation batches of IAT1+SAT1 to IAT8+SAT8 were composed of Sodium starch glycolate, Cros caremellose sodium and lactose as superdisintegrants with hydrating excipient in as immediate release layer of tablets and HPMC K4M as a hydrophilic polymer, Chitosan as bio adhesive polymer and guar gum as natural gum in sustained release part of tablets. The release profile depicted in figures and ie, IAT1+SAT1 to IAT4+SAT4 shows that Xanthum Gum, Guar gum and Carboxy methyl cellulose was helpful in retarding drug release. Batches from IAT5+SAT5 to IAT8toSAT8 were composed with HPMC K15, Chitosan and Guargum. From this experimental results it was observed that IAT8+SAT8 is considered as optimized formulation and released 89.95% drug at the end of 12hr as sustained release formulation with reproducibility.

MECHANISMS OF DRUG RELEASE

Curve fitting analysis

The results of dissolution data were suitable to various drug release kinetic equations. Higher correlation coefficient(r value) was found in Higuchi model.

Korsemeyer-Peppas model indicates that release mechanism does not provide proper result. The ‘n’ value could be used to characterize different mechanisms as:

Table No. XXX Mechanism of drug release.

N	Mechanism
0.5	Fickian diffusion(Higuchi matrix)
0.5<n<1	Non-Fickian diffusion
1	Case II transport

CONCLUSION

Pre formulation studies on Atenolol corroborate with the reported literature limits. FTIR studies revealed no chemical interaction and indicating stability of Pre formulation studies.

The results are reported in the present study ‘n’ value ranges between 0.13 to 0.32 for all batches indicated that the drug release occurred via Fickian diffusion. According to Higuchi model, the release of drug from matrix is directly proportional to square root of time and explains the Fickian diffusion. It may be coincident. However, n values of Korsmeyer-Peppas strongly indicates that diffusion mechanism is Fickian (Higuchi matrix).

To study the release mechanism of bilayer matrix tablets, different formulations were applied to various *in-vitro* dissolution model. The kinetic models included zero order, first order,

Higuchi and Korsmeyer-Peppas equations. As observed from the Table no: 18 the values of correlation-coefficient (r^2) for all the formulations were high enough to evaluate the drug dissolution behaviour by equation. Kinetic results revealed that, the formulations IAT1+SAT1 to IAT8+SAT8 followed first order kinetics as correlation coefficient(r^2) values(0.934-0.985) were higher than that of zero order release kinetics, indicating that diffusion, and erosion were involved in the release process. The formulations (IAT7+SAT7 and IAT8+SAT8) followed Korsmeyer-Peppas release as correlation coefficient (r^2) values between 0.987-0.973, indicating that erosion and diffusion involved in the release process. The formulation (IAT8+SAT8) followed Peppas release as correlation coefficient (r^2) value 0.973, indicating that erosion and diffusion involved in the release process.

The screening of super disintegrants by direct granulation method for IM layer and polymers with wet granulation method for SR layer was suitable.

The preparation of bilayer tablets were suitable and it was found to reproducible.

The evaluation parameters of hardness, friability, weight variation, drug content and *in-vitro* release for the formulation F1-F8 were found uniform and reproducible.

The release profile of bilayer matrix tablets containing SSG,CCS in immediate release HPMC K15,Chitosan and Guargum in sustained release formulae (IAT8+SAT8) which has given 89.95% release. Hence as the polymer ratio increase drug release will increase.Hence, bilayer matrix tablets containing SSG, CCS in immediate release HPMC K15, Chitosan and Guargum in Sustained release formulae (IAT8+SAT8) showed promising results. Found to be robust and reproducible.

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