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Original Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE BILAYER TABLETS OF PROPRANOLOL HYDROCHLORIDE

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ABSTRACT

Objective: The present study was to formulate and evaluate of sustained release bilayer tablets of anti-hypertensive drugs Propranolol hydrochloride.

Methods: The tablets were prepared by direct compression method by using superdisintegrants Sodium Starch Glycolate (SSG) for immediate release layer and mucoadhesive materials such as Hydroxy Propyl Methyl Cellulose (HPMC-K4M) and Carbopol 934 P for sustained release layer which could release the drug up to 12 hours in predetermined rate. Poly vinyl Pyrrolidone (PVP) K-30 was used as binder. The blends were evaluated for physicochemical parameter such as bulk density, tap density, compressibility index and angle of repose. The tablets were evaluated for post compression parameter such as hardness, thickness, diameter, weight variation, drug content uniformity and friability. *In vitro* drug release studies were performed by using USP type II apparatus (paddle method). The FTIR study revealed that there was no chemical interaction between drug and excipients.

Results: The formulation ME5 containing HPMC-K4M and Carbopol 934 P in the ratio of 3:1 gave an initial burst effect and followed by sustained release of drug without disintegration up to 12 hours.

Conclusion: The optimized formulation ME5 showed the best drug release profile up to 12 hours and fulfilled the many requirements reduced dosing frequency, increase the bioavailability and provide better patient compliance.

Keywords: Propranolol hydrochloride, Mucoadhesive materials, Sustained release bilayer tablet.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs [1]. Many orally-administered drugs display poor bioavailability when administered as the conventional dosage form. i.e. the rate and extent to which the drugs are absorbed is less than desirable. With several drugs, absorption may be as little as 30% or less of the orally administered dose. In addition, poorly absorbed drug often display large inter- and intra subject variability in bioavailability. This problem may be overcome by modified release drug delivery system with prolonged residence time in the stomach [2].

Besides this, Conventional dosage form produces the wide range of fluctuation in drug concentration in the blood stream and tissues which leads to reduction or loss in drug effectiveness or increase incidence of side effects with subsequent undesirable toxicity and poor efficiency. However, sustained or controlled drug delivery systems can decrease the frequency of the dosing and also increases effectiveness of the drug by localization at the site of action, reducing the dose required and providing uniform drug delivery [3].

Muco adhesive bilayer tablet is new concept for successful development of the sustained release formulation along with various features to provide a way of successful drug delivery system that include an immediate release (IR) layer and an sustained release (SR) layer. Immediate release layer provide therapeutically effective plasma drug concentration for a short period of time and sustained release (SR) layer maintain uniform drug levels over a sustained period to reduce dosing intervals and side effects, increase the safety margin for highly-potent drugs and thus offer better patient compliance.

Hypertension may be defined as a repeatedly elevation of blood pressure exceeding 140 over 90 mmHg-a systolic pressure above 140 mmHg with a diastolic pressure above 90 mmHg. It can cause blood vessel changes in the back of the eye (retina), abnormal thickening of the heart muscle, kidney failure, brain damage, myocardial infarction (heart attacks), heart failure, aneurysms of the arteries (e. g. aortic aneurysm), peripheral arterial disease [4].

Propranolol hydrochloride is a nonselective beta adrenergic blocking agent, is widely used in the treatment of hypertension, angina pectoris and many other cardiovascular disorders [5]. The oral bioavailability of Propranolol hydrochloride is low (15%-23%). It is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.80 [6]. It is highly water soluble drug with relatively short biological half-life of 3-5 hours and usual dose is 40 mg thrice daily. This demands high frequency of administration resulting in oscillation of plasma drug concentration, it is necessary to develop sustained release dosage form to reduce frequency of administration and to increase the efficacy and oral bioavailability of the drug.

The aim of the present study was to formulation and evaluate of sustained release bilayer tablet of Propranolol hydrochloride in which the immediate release layer will release the drug within 10 minutes and sustained release (SR) layer will maintain uniform drug levels over a sustained period of time. In formulation of sustained release layer, different hydrophilic materials such as HPMC K4M and Carbopol 934 P were used. The effect of combination of HPMC K4M and Carbopol 934 P were studied on in-vitro release.

MATERIALS AND METHODS

Propranolol hydrochloride was received as a gift samples from Glenmark pharmaceuticals Ltd, Nashik. Carbopol 934 P (CP), Hydroxy Propyl Methylcellulose (HPMC-K4M), polyplasdone, Sodium Starch Glycolate (SSG) and Poly Vinyl Pyrrolidone(PVP)K-30 were obtained from Loba Chemie Pvt. Ltd. Mumbai. All other reagents and chemicals used were of analytical grade.

Evaluation of powder blends

Bulk Density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in

to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The bulk densities (BD) of powder blends were determined using the following formula.

Bulk density=Total weight of powder/Total volume of powder

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities (TBD) of powder blends were determined using the following formula [8].

TBD= Total weight of powder/Total volume of tapped powder

Carr's compressibility index [7]

The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend. A quantity of 2g of blending from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25±2 per min to measure the tapped volume of the blend. The bulk density and tapped density were calculated by using the bulk volume and tapped volume. Carr's compressibility index was calculated by using the following formula.

Carr's compressibility index (%) = [(Tapped density-Bulk density) X100]/Tapped density

Hasner's ratio

The ratio of tapped density to bulk density of the powders is called the Hasner's ratio.

Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured. The angle of repose was calculated using following formula [9].

Tan Θ= h/r

Where, "h" is height of the heap and "r" is the radius of the heap of granules.

Preparation of bilayer tablet

The bilayer tablets of Propranolol hydrochloride were prepared by the direct compression method. The tablets were punched by using 8 stations, singles rotary tablet compression machine. The drug, polymers and other excipients used for both immediate (IR) and sustained release (SR) layers were passed through sieve # 80 before their use in the formulation.

CALCULATION

For sustained drug release up to 12 hours, the immediate dose of drug was calculated from total dose of Propranolol hydrochloride extended release tablet, which was 80mg. According pharmacokinetic data [10]

Dt = Dose $(1+0.693 \times t/t_{1/2})$ Where, Dt = Total dose, Dose = Immediate release dose, t = Total time period for which sustained release is required, $t_{1/2}$ = Half-life of drug. Half-life of Propranolol hydrochloride ranges from 3 to 5 hours.

For example,

i. Propranolol hydrochloride: 80 = Dose [1+(0.693 ×12)/3)], Dose = 21.208 mg Propranolol hydrochloride.

ii. Propranolol hydrochloride: 80 = Dose [1+(0.693 ×12)/5)], Dose = 30.039 mg Propranolol hydrochloride.

According to dose calculation, IR dose of drug can be taken in between range of 21.208 mg to 30.039 mg for the preparation of bilayer tablets; thus 25 mg of Propranolol hydrochloride was taken in IR layer and 55 mg of Propranolol hydrochloride was taken in SR layers.

Formulation of the IR layer [11, 12]

The IR ingredients (Table 1) were accurately weighed and added into the blender in ascending order. The powder mixture was blended for 20 minutes to obtain uniform distribution of the drug in formulation. The blend was mixed with talc and magnesium stearate for 2 minutes and kept in desiccators until further used.

Formulation of the SR layer

The SR ingredients were accurately weighed and added into the blender in ascending order. The powder mixture was blended for 20 minutes to obtain uniform distribution of the drug in formulation and subjected for pre-formulation studies.

Compression of bilayer tablet

In the present study bilayer tablet was prepared manually using single station punching machine

(Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat). Accurately weighed amount of SR powder mixture was fed manually into die cavity. SR layer was compressed at mild compression force (2-3 kg/cm^2). After that accurately weighed IR powder mixture was manually fed into the die on SR layer and compressed using 9 mm circular punches (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat). Both the layers were identified on the basis of color since the immediate release layer had pink color and the sustained release layer has white color.

Evaluation of bilayer tablets

Hardness test

Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland) was used to determine the crushing strength. 6 tablets were randomly selected from each formulation and the pressure at which each tablet crushed was recorded.

Friability test

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (w_0 initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w). The % friability was then calculated by,

$$\textbf{Percentage of Friability} = 100\ (1\text{-}w/w_0)$$

Percentage friability of tablets less than 1% is considered acceptable.

Uniformity of weight

20 tablets from each of the formulation were weighed individually with an analytical weighing balance (Model: AY-200, SHIMADZU Corporation, JAPAN). The average weights for each brand as well as the percentage deviation from the mean value were calculated.

Drug content uniformity [13]

Ten tablets were finely powdered and an amount equivalent to 100 mg of Propranolol hydrochloride was accurately weighed and transferred to a 100 ml volumetric flask, then 70 ml of buffer pH 1.2 (0.01N HCl) was added. The flask was shaken for 10 minutes. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered through Whatman filter paper (No.41) and 1 ml of the filtrate was suitably diluted up to 100 ml with same buffer solution and analyzed for Propranolol hydrochloride content at 290 nm using a double beam UV/Visible spectrophotometer (Shimadzu 1800, Japan) and 0.01N Hcl as blank.

***In-vitro* dissolution studies**

The release rate of Propranolol hydrochloride bilayer tablets was determined by using Dissolution testing apparatus USP type II (Paddle type) (Electro lab). The dissolution testing was performed

using 900 ml of 0.1N HCl at 37±0.5°C temperature and speed 50 rpm. The 5 ml aliquots were withdrawn at intervals of 5, 10, 15, 20, 25, 30, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660, 720 minutes and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Each 5 ml aliquot was filtered through Whatman filter paper (No.41). 5 ml of the sample was diluted to 10 ml 0.1N hydrochloric acid for first 2 hours and then with pH 6.8 phosphate buffers for next 10 hours and absorbance was measured at 290 nm using UV/Vis spectrophotometer (JASCO V-550).

Drug concentrations in the sample were determined from the standard calibration curve.

RESULTS AND DISCUSSION

Optimization of the effect of super disintegrants in immediate release layer of bilayer tablet

Different formulations were made in order to achieve the desired drug release from the IR layer of the bilayer tablet. The formulae were as follows.

Table 1: Pre-compression parameter of immediate release formulations

Composition	Weight per tablet (mg)					
	MI1	MI2	MI3	MI4	MI5	MI6
Drug	25	25	25	25	25	25
Polyplasdone	5	6	7	-	-	-
SSG	-	-	-	5	6	7
D. C. P	55.8	54.8	53.8	55.8	54.8	53.8
PVP-30	10	10	10	10	10	10
Talc	2	2	2	2	2	2
Mg-Stearate	2	2	2	2	2	2
Color	0.2	0.2	0.2	0.2	0.2	0.2
Total Wt.	100	100	100	100	100	100

Table 2: Formulation development of immediate release layer

Composition	Weight per tablet (mg)
Propranolol hydrochloride	25
Sodium starch glycolate(SSG)	6
PVP-K30	10
D. C. P	54.8
Talc	2
Mg-Stearate	2
Color	0.2
Total Wt.	100

Table 3: Formulation development of sustained release layer

Composition	Weight per tablet (mg)					
	ME1	ME2	ME3	ME4	ME5	ME6
PRO-HCL	55	55	55	55	55	55
HPMC-K4M	30	30	30	30	30	30
Carbopol	30	25	20	15	10	5
PVP-K30	20	20	20	20	20	20
D. C. P.	57	62	67	72	77	82
Talc	4	4	4	4	4	4
Mg-Stearate	4	4	4	4	4	4
Total Wt.	200	200	200	200	200	200

Table 4: Micromeritic properties of pre-compression powder blend

Code	Bulk density (gm/ml)	Tapped density(gm/ml)	Carr's index. (%)	Hausner's ratio	Angle of repose (θ)
ME1	0.363	0.416	14.60	1.14	24.34
ME2	0.337	0.400	10.70	1.18	23.80
ME3	0.327	0.384	14.84	1.17	22.52
ME4	0.333	0.386	13.80	1.15	21.80
ME5	0.327	0.370	11.60	1.13	21.54
ME6	0.384	0.454	13.50	1.18	16.82

Table 5: Post-compression parameter of sustained release bilayer tablets

Code	Dimension		Hardness (kg/cm^2)±SD	Friability (%)±SD	Weight variation (gm)±SD	Drug content (%w/w)±SD
	Diameter (mm)±SD	Thickness (mm)±SD				
ME1	9.46±0.031	4.82±0.024	5.24±0.061	0.12±0.017	299±1.40	99.3±0.3
ME2	9.44±0.026	4.80±0.035	4.87±0.045	0.13±0.018	302±1.38	100.1±0.4
ME3	9.51±0.023	4.87±0.022	4.45±0.034	0.20±0.021	298±1.45	98.4±0.2
ME4	9.52±0.017	4.91±0.026	4.29±0.032	0.26±.012	301±1.41	101.3±0.5
ME5	9.49±0.039	4.87±0.031	4.17±0.047	0.31±0.015	300±1.46	99.6±0.4
ME6	9.47±0.038	4.79±0.013	4.02±0.036	0.41±0.025	303±1.52	99.1±0.6

Formulation of batches of bilayer tablet

The various formulations were prepared by varying the quantity of polymers and also by using different polymers to study the dissolution profiles. The manufactured tablets were evaluated mainly for thickness, hardness and percent drug release.

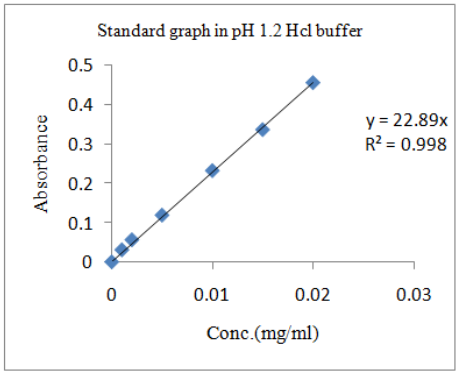


Fig. 1: Calibration curve of Propranolol Hcl in 0.1N Hcl Buffer

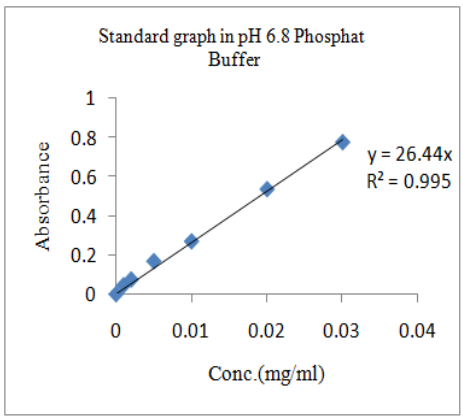


Fig. 2: Calibration curve of Propranolol Hcl in 6.8 pH Phosphate

Determination of λmax and development of calibration curve of Propranolol hydrochloride

Maximum absorbance (λmax) of Propranolol hydrochloride were measured at pH 1.2 (hydrochloric acid buffer) and pH 6.8 (phosphate buffer) using UV/Vis spectrophotometer (JASCO V-550). Calibration curves were prepared using concentration ranges of 1–25 mcg/ml for pH 1.2 and 1-30 mcg/ml for pH 6.8.

The prepared bilayer tablets were evaluated for various physical properties. The bulk density of various formulations ranged between 0.32 and 0.38 gm/ml and tapped density between 0.38 gm/ml to 0.48 gm/ml. This value of bulk density indicates of good packing character. The compressibility Index (CI) for all formulations was found to be below 15% indicating excellent compression properties. The flow properties of blends were further analyzed by determining the angle of repose for powders. It ranged between 16.82±0.38 to 24.34±0.26. The value indicates good flow property of powders. All the batches of tablets were produced under similar conditions to avoid processing variable. Average weight of tablets was 300±1.4 mg, hardness was 4.50±.042 kg/cm^2 and thickness was 4.84±0.1 mm. The percentage friability of all formulation was 0.23±0.01%. Values of hardness test and percentage friability indicate good handling properties of the prepared bilayer tablets. The drug content uniformity in bilayer tablets was 99.6%±0.4.

FT-IR spectrum of Propranolol hydrochloride bilayer sustained release tablets revealed there was no major interaction between drug and polymers used in the study. The release of Propranolol hydrochloride from fast releasing layer was analyzed by plotting the cumulative percent drug release Vs time. It showed an effective initial burst effect from IR layer. From all the formulation over 30% of Propranolol hydrochloride were released within 10 minutes.

Formulations ME1, ME2, ME3, ME4, ME5 and ME6 were prepared by using HPMC K4M and Carbopol 934 P. In each formulation the quantity of HPMC K4M was 15% but the quantity of Carbopol 934 P was varied to achieve the desired drug release profile. In formulation ME1 the quantity of Carbopol 934 P was 15%w/w which gave drug release of 82.42% after 12 hours. In order to achieve greater drug release in formulation ME2, ME3, ME4 and ME5 the quantity of Carbopol 934 P was reduced to 12.5%, 10%, 7.5% and 5% the drug release from the formulation was found to 85.48%, 91.61%, 93.71% and 98.33% after 12 hours. When the quantity of Carbopol 934 P was reduced to 2.5% in formulation ME6, the drug released from the formulation 100% within 10 hours. This formulation (ME6) was unable to sustain the drug over 12 hours. The formulation ME5 containing15% of HPMC K4M and 5% of Carbopol 934 P was selected as the optimized batch since it showed the best drug release profile up to 12 hours as compared to the other formulations. In this selected formulation, the calculated regression coefficient for Higuchi and Peppas's models were 0.982 and 0.980 respectively. Higuchi's Plot, Peppas's Plot states that release followed the diffusion controlled mechanism. All the other parameters of the batch ME5 were found to be satisfactory.

Table 6: Dissolution release profiles of formulations (ME1-ME6)

S. No.	Time (minutes)	Cumulative % drug release					
		ME1	ME2	ME3	ME4	ME5	ME6
1	5	28.33±0.16	30.67±0.14	31.82±0.21	31.31±0.15	30.93±0.11	32.08±0.12
2	10	30.02±0.51	32.76±0.32	35.70±0.54	35.10±0.56	32.36±0.31	36.51±0.51
3	15	31.97±0.91	34.56±0.87	38.75±0.42	36.53±0.63	33.47±0.53	38.03±0.91
4	20	34.75±0.47	36.07±0.21	40.58±0.64	37.03±0.81	36.14±1.32	39.47±0.47
5	25	37.19±0.73	38.01±0.33	41.69±0.83	39.36±0.73	37.86±0.65	41.43±0.73
6	30	39.86±0.77	40.34±1.17	43.84±1.03	41.28±0.62	38.62±1.98	43.62±0.77
7	60	45.82±0.98	43.96±0.98	47.95±0.96	48.90±1.51	45.75±1.65	53.28±0.89
8	120	50.75±0.41	49.95±0.58	56.08±2.55	56.83±1.08	56.88±2.55	63.24±0.41
9	180	58.86±0.79	58.55±1.44	66.84±1.83	68.67±1.76	69.95±1.78	75.12±0.79
10	240	61.81±1.51	63.41±0.47	72.26±0.82	75.81±2.62	76.27±1.22	79.23±1.51
11	300	64.87±1.78	67.52±0.68	77.16±2.54	77.69±2.81	80.36±0.87	83.86±1.78
12	360	67.11±0.83	70.51±0.91	79.20±1.42	81.15±1.53	84.42±2.98	87.40±0.83
13	420	68.67±0.67	71.90±0.54	80.80±0.52	83.98±3.58	87.08±1.90	91.61±0.67
14	480	70.98±0.82	73.89±2.32	83.98±5.15	85.41±1.04	89.11±1.75	94.15±0.82
15	540	73.60±0.69	78.00±0.39	85.66±2.52	86.30±1.33	91.55±0.78	97.56±0.69
16	600	76.76±1.74	80.93±0.41	86.55±1.57	89.46±5.71	93.26±1.44	100.00±1.74
17	660	79.22±0.63	83.04±0.78	88.78±3.41	91.70±3.65	95.81±2.73	95.12±0.63
18	720	82.42±3.32	85.48±1.12	91.61±1.39	93.71±2.73	98.33±1.64	91.30±3.23

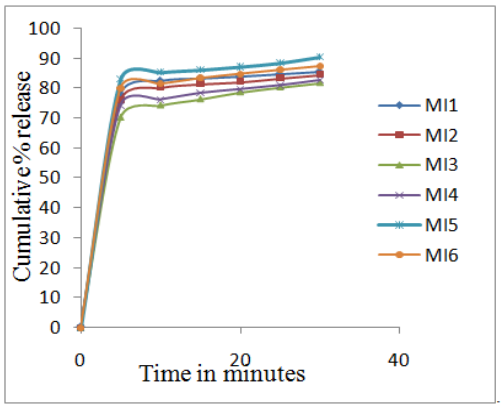


Fig. 3: Dissolution profiles of formulation MI1-MI6

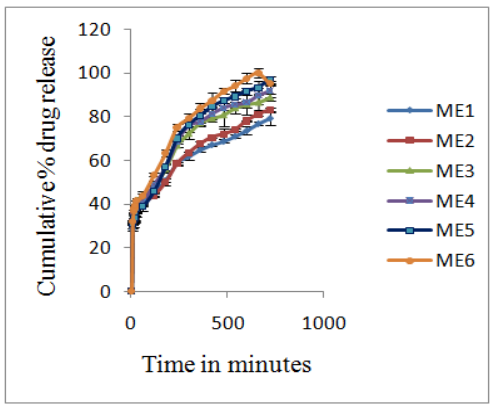


Fig. 4: Dissolution profiles of formulation ME1-ME6

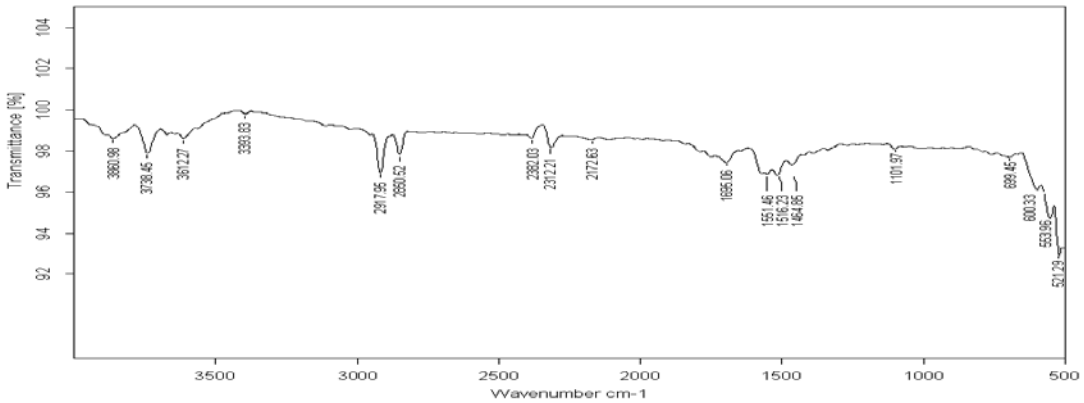


Fig. 5: IR Spectra of Propranolol hydrochloride

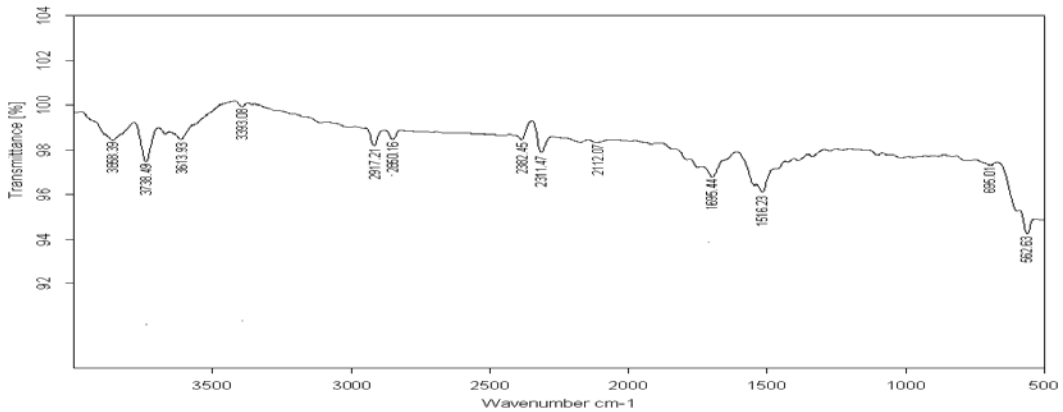
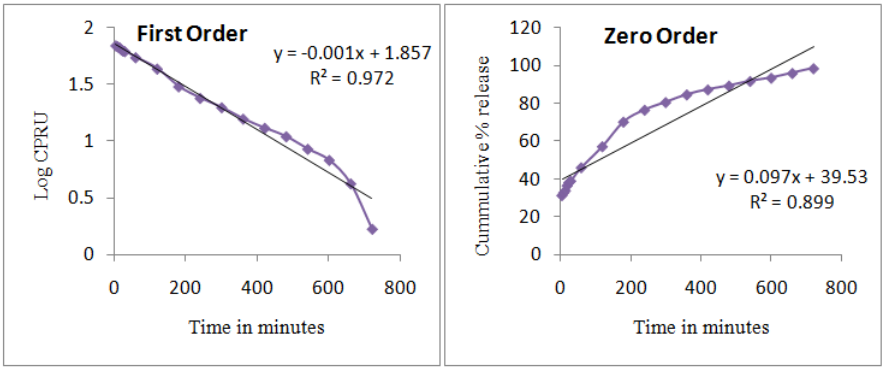


Fig. 6: IR Spectra of formulation ME5



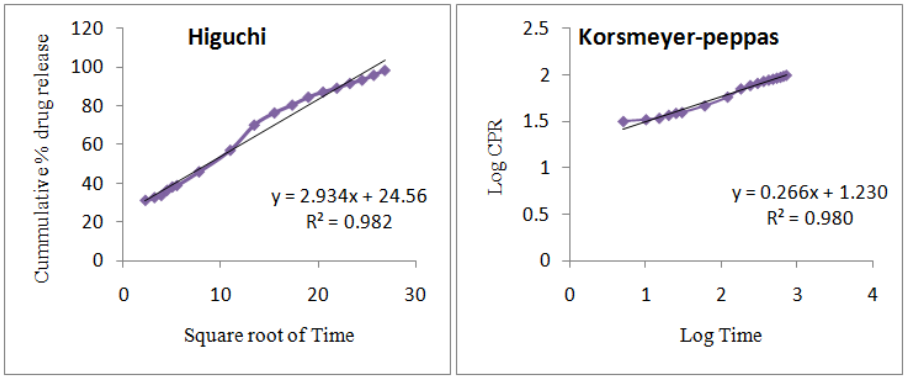


Fig. 7: Release kinetics of optimized formulation ME5

CONCLUSION

The present research was carried out to develop a bilayer tablet of Propranolol hydrochloride using superdisintegrant sodium starch glycolate for fast release layer and combination of HPMC K4M and Carbopol 934 P for sustaining release layer. The tablets showed an initial burst release to provide the loading dose of the drug followed by sustained release up to 12 hours. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance.

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CONFLICT OF INTERESTS

Declared None

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