INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

FORMULATION AND EVALUATION OF BILAYER TABLET OF METOPROLOL SUCCINATE AND CHLORTHALIDONE

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ABSTRACT

In present study, an attempt was made to prepare bilayer tablet of Metoprolol Succinate and Chlorthalidone. Bilayer tablet concept has been investigated to develop combination of sustained and immediate released tablet. Metoprolol Succinate is a $ß_1$-selective adreno-receptar blocking agent with half life3-4 hrs. Chlorhtalidone is an oral antihypertensive/ diuretic, due to its limited aqueous solubility bioavaibility is low. To improve bioavaibility and solubility, Inclusion complex of Chlorthalidone was prepared with Hydroxy propyl ß- Cyclodextrin. Sustained release of metoprolol tablet was formulated by using synthetic (HPMC E15) and natural (*moringa oliefera* gum) polymer in different concentrations, nine formulations were prepared at three levels (+1, 0, -1) of polymer concentration. Immediate release tablet of Chlorthalidone were formulated by using sodium starch glycolate and crosspovidone, four batches were formulated at two level (+1, -1) of polymer concentration. Batches of formulation were formulated by using Design expert10 software. The formulations are made by employing the direct compression method. The tablets were subjected to weight variation test, drug content, hardness, friability, and *in-vitro* release studies, release kinetics of sustained release tablet. Among all formulation, F8 batch of metoprolol Succinate tablet containing high concentration of polymers showed 12hrs release and F1 batch of Chlorthalidone showed good released in 35min.

Keywords: Metoprolol succinate, Chlorthalidone, bilayer tablet.

INTRODUCTION

Tablet is a solid pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compressed form a powder into a solid dose. Over the past 30 years, as the expense and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained release or controlled release drug delivery systems.[1]

Metoprolol Succinate is a cardio selective ß-blocker that has been classified as a class I substance according to the Biopharnaceutics Classification Scheme, meaning that it is highly soluble and highly permeable. The drug is readily and completely absorbed throughout the whole intestinal tract but is subject to extensive first pass metabolism resulting in incomplete bioavaibility (about 50%). After a single oral dose, peak plasma concentration occurs after about 1-2 hours. The drug is eliminated within 3 to 4 hours, which depending on therapeutic intension, makes it necessary to administer simple formulations of metoprolol up to 4 times daily. To avoid these and for better patient compliance Metoprolol Succinate sustained release tablet was formulated. Dosing interval typically reduced to once or twice a day.[2]

MATERIALS AND METHODS

Metoprolol succinate and Chlorthalidone was a gift sample from Ajanta Pharmaceutical, Aurangabad and IPCA laboratories respectively, Mumbai. HPMC–E-15, Avicel-102, Crosspovidone, Sodium starch glycolate, magnesium stearate, Talc was obtained from Modern Science Pvt. Ltd, Nashik.

Method

Drug and Excipients Compatibility Studies

UV spectroscopy

The both drugs were scanned in UV Spectrophotometer to detect the λmax and to draw the calibration curve of the drug in water, phosphate buffer (pH 6.8) and in methanol as a solvent. The drugs were used in concentration ranges of 20-45 and 5-25 ppm of Chlorthalidone and Metoprolol Succinate respectively. The spectra and calibration curve of both the drugs are as shown in **Figure 1, 2, 3, 4, 5 and 6 respectively.**

FTIR spectral studies

The infrared spectra of Metoprolol Succinate and Chlorthalidone were recorded by SHIMADZU 84005 FTIR spectrometer, equipped with an Inferometer detector. Samples were prepared by KBr disc method (2 mg sample in 100 mg KBr) and examined in the transmission mode. Each spectrum was measured over a frequency range of 4000–400 cm^{-1}.

The spectra shown in **Figure 7, 8 respectively.**

DSC studies

DSC analysis was performed using Shimadzu-Thermal Analyzer DSC 60 on 2-5mg samples. Sample was heated in an open nitrogen pan at a rate of 10°C/min conducted over a temperature range of 50 to 200°C for Metoprolol Succinate and Chlorthalidone under nitrogen flow of 2 bar pressure. The spectra shown in **Figure 12, 13respectively.**

Collection and evaluation of *moringa oliefera* gum

Collection[11,12]

The moringa oleifera tree located in Shirasgaon, in yeola Dist. Nashik was identified. The tree trunk was incised working from the base up towards the branches. The incisions were 10-15 mm long and 4-5 mm deep. The gum then started to seeping out from the incisions and coagulated in 10-20 days. When the gum was sufficiently dried it was collected and spread out to dry. The gum was collected from trees (injured site).

Evaluation of moringa oleifera gum[11,12]

(a) Loss on drying

The method adopted was that specified in the B.P 2004 for acacia. One gram of the sample was transferred into each of several Petri dishes and then dried in an oven at 105°C until a constant weight was obtained. The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage. The results are mentioned in **Table No.1.**

(b) pH determination

pH was determined by shaking a 1%w/v solution of the sample in water for 5 min and the reading were noted by digital pH meter. The results are mentioned in **Table No.1.**

(c) Tannin test

To the 10ml of 10%w/v solution of gum, then 0.1ml of ferric chloride test solution was added to it. Gelatinous precipitate formed but neither a precipitate nor liquid shows dark blue color nor result was reported. The results are mentioned in **Table No.1.**

(d) Starch test

The 10 ml of 10%w/v solution was prepared. To it 0.1 ml of 0.005M Iodine was added. The results are mentioned in **Table No.1.**

(e) Sucrose and fructose test

To 1 ml of 10% w/v solution. To it the 4 ml of distilled water was added then to it 0.1 gm of resorcinol and 2 ml of hydrochloric acid was added. The results are mentioned in **Table No.1.**

(f) Swelling power test

A 1 gm of transfered to 100 ml measuring cylinder containing 90ml of water, shake well for 30 seconds and allow to stand for 24 hours, shaking gently on 3 occasions during this period .The sufficient water was added to produce 100 ml, mixed gently for 30 seconds, avoiding the entrapment of air, allow to stand for 5 hours and measured the volume of mucilage. The determination was repeated for three times. The results are mentioned in **Table No.1.**

Preparation of Metoprolol Succinate sustained release tablet

Different formulas (Table No.2, 3) were prepared to achieve good sustained release action of Metoprolol succinate by using HPMC E-15 and Moringa oliefera gum in different ratios.

The granules were prepared by wet granulation technique.

Wet granulation

All excipients were weighed separately. Accurately weighed quantity of Metoprolol Succcinate & polymers (HPMC E15 & Moringa oliefera) were mixed thoroughly in mortar & granulated using 10% w/v starch solution as a binder. The granules so obtained were placed in oven at 60ºC for 2 hr. These granules were again passed through 22 mesh sieve after getting dry. The fine granules formed are then lubricated with 0.5% w/w Magnesium stearate. The flow properties were determined. These granules were then compressed into tablet (each 200mg) using mm concave punch of 10 station shiv pharma ETBC 1974 machine.

Formula design

Formulas were design by 3^2 factorial design, nine batches were formulated. Three levels (+1, 0, -1) and two polymers (HPMC E15 and *Moringa oliefera*) were selected and master formula were prepared. Final weight of sustained release tablets were adjusted to 200mg. Master formulas with quantities is as shown in **Table No. 2, 3.**

Evaluation parameters (Metoprolol Succinate sustained release tablet)

Evaluation of pre compression parameters of the powder blends.

Pre-compression parameters of the prepared blend of all the formulations were studied by determining the Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose. The results are shown in **Table No. 7.**

Evaluation of post compression parameters of the powder tablets[14,15,16]

The compressed Metoprolol Succinate sustained release tablet were subjected to various physical tests which include hardness, friability, weight variation, thickness and drugs content uniformity. The results are shown in **Table No. 8.**

Hardness test[14,15,16]

For each formulation, the hardness of three tablets was checked using the Monsanto hardness tester (LAB- HOSP) average values are shown in **Table No.8.**

Thickness [14,15,16]

The thickness of tablet is important for uniformity of tablet size. The thickness of the tablets was determined using a Vernier Calliper. Three tablets from each batch were used, and average values are shown in **Table No 8.**

Friability[14,15,16]

Friability is the measure of tablet strength. In this test, number of tablets subjected to combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25rpm, dropping the tablets at a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche Friability tester (Kumar Mfg. Ltd.) This was then operated for 100 revolutions. The tablets then deducted and reweighed. Permitted friability limit is 1.0%. Tablets were then weighed and friability values were determined and are reported in **Table. No. 8**.

$$\text{Friability} = (W2 - W1 / W1) \times 100$$

Where W1 is the initial weight and W2 is the final weight of the tablets.

Weight variation[14,15,16]

Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The percent deviation was calculated using the following formula and reported in **Table No.8**.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Drug Content Uniformity Study[14,15,16]

Five tablets were weighed individually and powdered. The powder equivalent to 10 mg of Metoprolol succinate was weighed and dissolved in small amount of phosphate buffer (pH 6.8). The volume was made to 100 with phosphate buffer (pH 6.8). From this stock solution, 25 µg/ml dilution was prepared. The drug contents of the resulting solution were calculated from UV absorbance at 222 nm. Results are mentioned in **Table No. 8**.

Swelling index test[11,13]

The extent of swelling was measured in terms of percentage weight gain by the tablets. The swelling behaviour of all the formulation was studied. One tablet from each formulation was kept in petri plate containing phosphate buffer pH 6.8. at the end of 2,4, 6,8, 10 and 12hrs tablets were withdrawn, soacked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using formula.

$$SI = \frac{Mt - Mo}{Mo} \times 100$$

Where, SI = Swelling index
Mt = Weight of tablet at time‘t’ and
Mo = Weight of tablet at time ‘0’
The results are mentioned in **Table No.8**.

***In - vitro* Drug Release Study**[6,13,]
The release rate of Metoprolol succinate sustained release matrix tablets was determined using United States pharmacopoeia (USP) Dissolution testing Apparatus 2 (paddle method). The dissolution test was performed using 900ml of Phosphate buffer pH 6.8, at 37 ± 0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. The samples were filtered through filter paper. Absorbance of these solutions was measured at 222 nm using a UV/ Visible Spectrophotometer. The drug release was plotted against time to determine the release profile. The results are mentioned in **Table No.9.**

Drug release kinetics[,13,14.16]
All formulations were subjected to various mathematical kinetic models like Zero-order, First-order, Higuchi, Korsmeyer-Peppas to understand the release patterns and establish the kind of mechanism followed by Metoprolol Succinate release from tablet. Results are reported in **Table No.10.** and **Figure No.16,17.**

Solubility enhancement of Chlorthalidone
Solubility Study of Chlorthalidone
To determine solubility of Chlorthalidone, it was performed in water and Phosphate buffer pH 6.8. Solubility studies were carried out in glass vials. In each of these vials, 25 ml of each media were added. Excess quantity of drug (50 mg) was added into each of vials. These vials were shaken continuously for 24 hours on a lab shaker and the resulting solutions were filtered, appropriate dilutions were made and UV absorbances were recorded at 275nm.

Preparation of Inclusion complex of Chlorthalidone by kneading method[9,17]
Drug and Hydroxypropyl-β-Cyclodextrin in the proportion of appropriate molar ratio were mixed in a mortar for one hour with small quantities of methanol was added intermittently to get slurry like consistency. The paste was dried in the oven at the temperature of 45°C. Dried complex were pulverized into fine powder and sifted with sieve # 80.

Characterization of Inclusion Complex
Inclusion Complex of Chlorthalidone were characterized using following analytical techniques
a) Saturation solubility studies
b) Drug content estimation
c) FT-IR spectral analysis
d) Differential Scanning Calorimetry.

(a) Saturation Solubility Study[9,17]
Saturation solubility studies were carried out for all inclusion complexes prepared. This study was the basic criteria to identify and judge the inclusion complex of choice, which would enhance the solubility and so, would show good results in *in-vitro* dissolution studies. Solubility studies were carried out in glass vials. In each of these vials, 10 ml distilled water was added. Excess quantities of inclusion complex were added into each of vials. These vials were shaken continuously for 24 hours on a lab shaker and the resulting solutions were filtered, appropriate dilutions were made and UV absorbances were recorded at 257 nm. Result is shown in **Table No. 12**

(b) Drug Content[9,17]
About 10 mg drug equivalent of solid dispersion were weighed accurately and transferred to 100 ml volumetric flask to which 20 ml methanol was added and sonicated for 15 min. Final volume was made up with methanol. From this stock solution (100 µg/ml), 1 ml was withdrawn and further diluted up to 10 ml with methanol. This solution was used for the assay for drug content by UV spectrophotometer at 276 nm. Concentration of drug in stock solution was calculated by using calibration curve and from which percent drug content in solid dispersions was calculated.

$$\% \text{ Drug content} = \frac{W_A}{W_T} \times 100$$

Where, W_A= Actual drug content, and
W_T= Theoretical drug content.
Results are shown in **Table No. 13**

(c) FT-IR Spectroscopy[9,17]
Fourier transform infrared spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the inclusion complex on a FT-IR spectrophotometer by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000-400 cm^{-1} with a resolution of 4 cm^{-1}.peaks are shown in **Figure No. 11.**

(d) Differential Scanning Calorimetry (DSC) [9,17]

The possibility of any interaction between the drug and the carriers during preparation of inclusion complex was assessed by carrying out thermal analysis of drug alone as well as that of the optimized inclusion complex, using DSC. DSC analysis was performed using Shimadzu- Thermal Analyzer DSC 60 on 2-5 mg samples. Samples were heated in an open nitrogen pan at a rate of 10°C/min conducted over a temperature range of 30 to 315°C under a nitrogen flow of 10 ml/min.[37,39] Thermogram are as shown in **Figure No. 15.**

Formulation of immediate release Chlorthalidone Tablet

Factorial design

From the literature survey studies the concentration of Crosspovidone & Sodium starch glycolate were selected. Based on concentration 2 factors will be evaluated, each at 2 levels, & experimental trials will be performed at 4 possible combinations. The amount of Crosspovidone & Sodium starch glycolate was selected as independent variables. Four batches were formulated and evaluated for weight variation, disintegration, dissolution etc. test. Master formula is given in **Table No. 6.**

Evaluation of powder blends

Powder blend of IR tablet were evaluated for bulk density, tapped density, carr's Index, compressibility index, hausner's ratio and angle of repose as per procedure. Results are shown in table

Preparation of IR tablet

In IR tablet SSG and crosspovidone were used as a disintegrating agent, where avicel used as binder and diluent. Magnesium stearate used as lubricant. Weighed the quantity of drug and polymer, all ingredients were mixed properly. Magnesium stearate was added to lubricate the mixture. Preformulation study was done and IR tablets were formed by direct compression.

Evaluation of IR Chlorthalidone tablet

Weight Variation[14,15,16]

Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Results are mentioned in **Table No. 14.**

Thickness [14,15,16]

The thickness of tablet is important for uniformity of tablet size. The thickness of the tablets was determined using a Vernier Calliper. Three tablets from each batch were used, and average values are shown in **Table No. 14.**

Hardness [14,15,16]

For each formulation, the hardness of three tablets was checked using the Monsanto hardness tester (LAB- HOSP) average values are shown in **Table No. 14.**

Drug Content Uniformity Study[9,16]

Five tablets were weighed individually and powdered. The powder equivalent to 10 mg of Chlorthalidone was weighed and dissolved in small amount of phosphate buffer (pH 6.8). The volume was made to 100 with phosphate buffer (pH 6.8). From this stock solution, 25 µg/ml dilution was prepared. The drug contents of the resulting solution were calculated from UV absorbance at 222 nm. Results are mentioned in **Table No. 14.**

Friability[14,15,16]

Friability is the measure of tablet strength. In this test number of tablets subjected to combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25rpm, dropping the tablets at a distance of 6 inches in each revolution. A sample of pre weighed tablets was placed in Roche Friability tester (Kumar Mfg. Ltd.) This was then operated for 100 revolutions. The tablets then dedusted and reweighed. Permitted friability limit is 1.0%.Tablets was then weighed and friability values were determined and results are reported in **Table No. 14.**

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where,

W_1 = weight of the tablets before test,

W_2 = weight of the tablets after test

Disintegration test[14,15,16]

The *in-vitro* disintegration studies were carried out using Tablet Disintegration Test Apparatus. One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in one-liter beaker containing water maintained at 37±2^{0}C. The basket was then moved up and down through a distance

of 5 to 6 cm at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded. The test was performed for tablets of all type of formulation (F1-F4). The results are shown in **Table No. 14.**

Drug content uniformity[9,17]

One tablet was crushed and 25ml of methanol was mixed and shaken for 15 minutes. Sufficient water was added to produce 100 ml. Solution was filtered and the absorbance maxima of the resulting solution was recorded as 275 nm. The results are shown in **Table No. 14.**

***In-vitro* dissolution study6,9**

In vitro release of the tablets (Table-3) was conducted using USP dissolution apparatus II (UV-1700 Schimadzu Corporation, Japan) at 75 rpm, using phosphate buffer pH 6.8 and 0.1N HCl as a dissolution media maintained at 37±0.5°. Samples were withdrawn at various time intervals, diluted and assayed at 275 nm, using an UV/VIS spectrophotometer. All the results were performed in triplicate. The results are shown in **Table No. 15.**

RESULT AND DISCUSSION

The prepared tablets were evaluated for Weight variation, hardness, friability, thickness, drug content and dissolution studies. Results of all formulation of both Metoprolol Succinate sustained release tablet and Chlorthalidone Immediate release tablet were given in Tables.

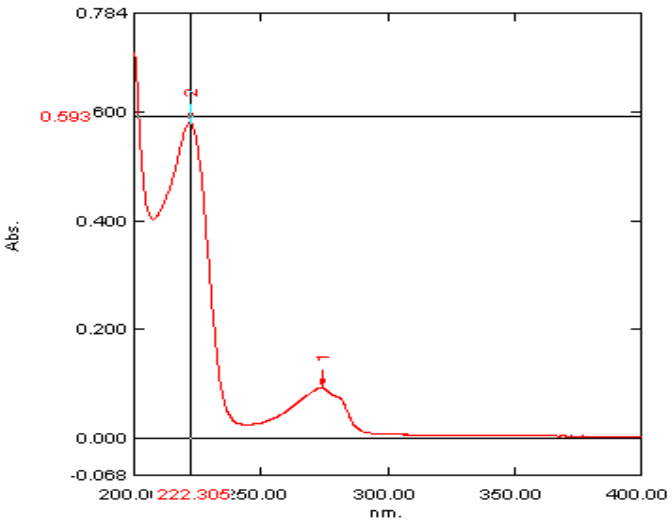

Fig. 1: UV Spectrum of Metoprolol succinate in Water

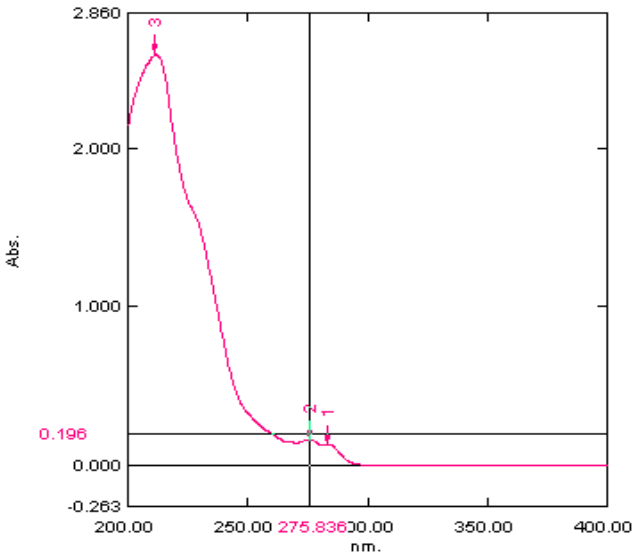

Fig. 2: UV Spectrum of Chlorthalidone in Methanol:Water

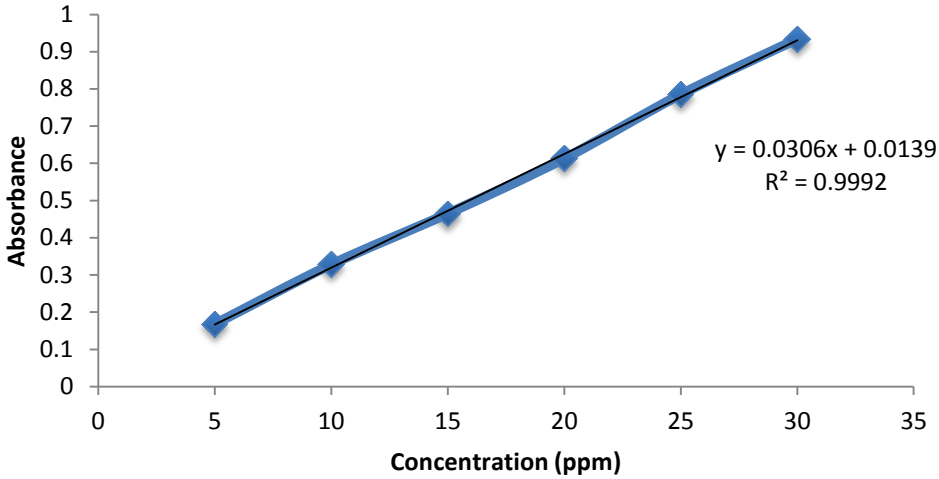

Fig. 3: Calibration Curve of Metoprolol succinate in Distilled Water

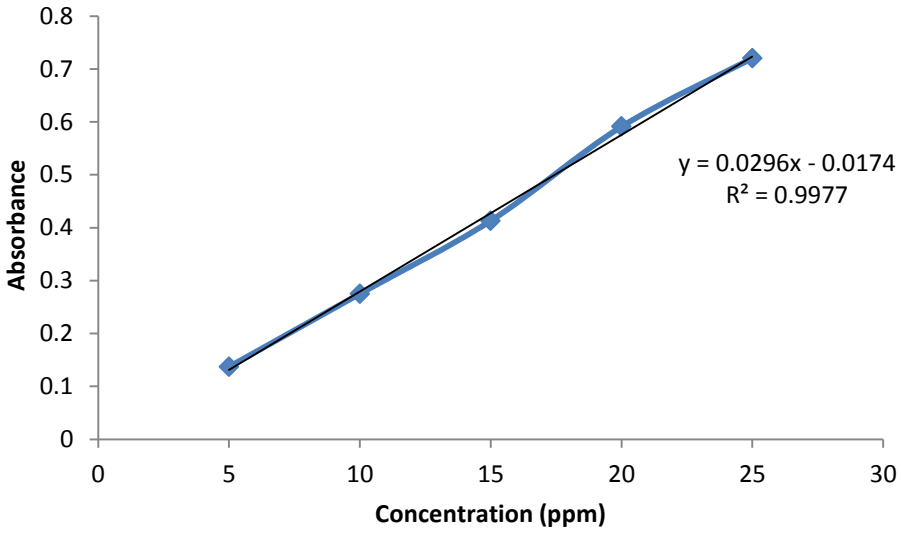

Fig. 4: Calibration Curve of Metoprolol succinate in Phosphate buffer pH 6.8

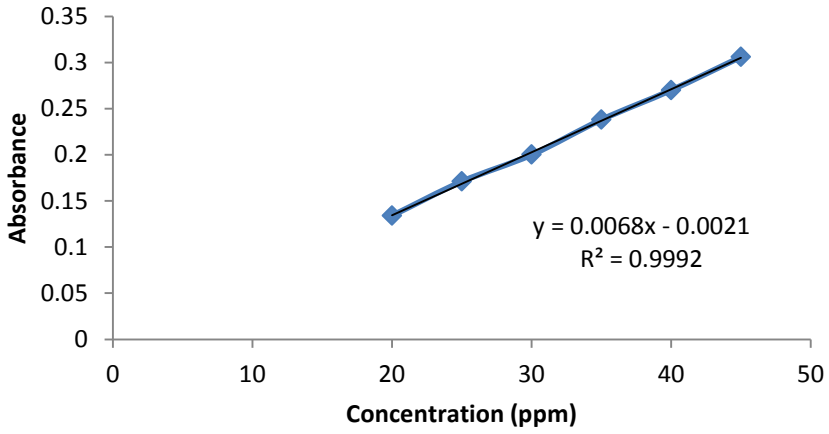

Fig. 5: Calibration Curve of Chlorthalidone in Methanol:Water

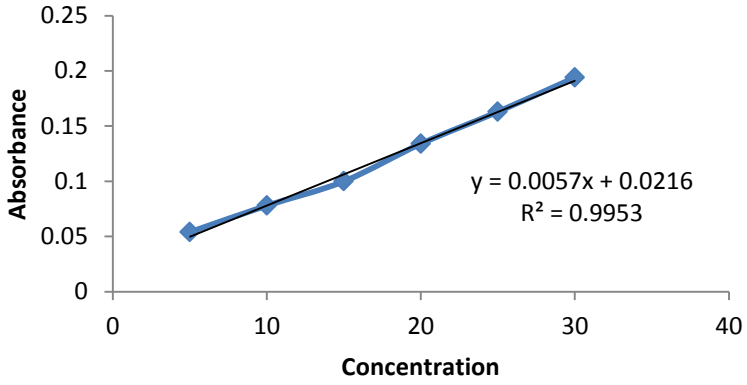

Fig. 6: Calibration Curve of Metoprolol succinate in Phosphate buffer pH 6.8

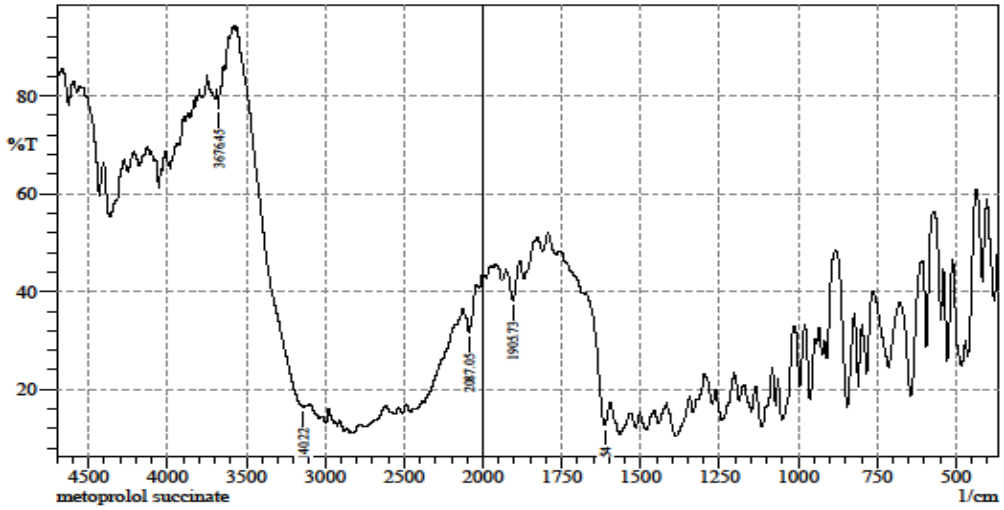

Fig. 7: IR spectrum of Metoprolol succinate (pure drug)

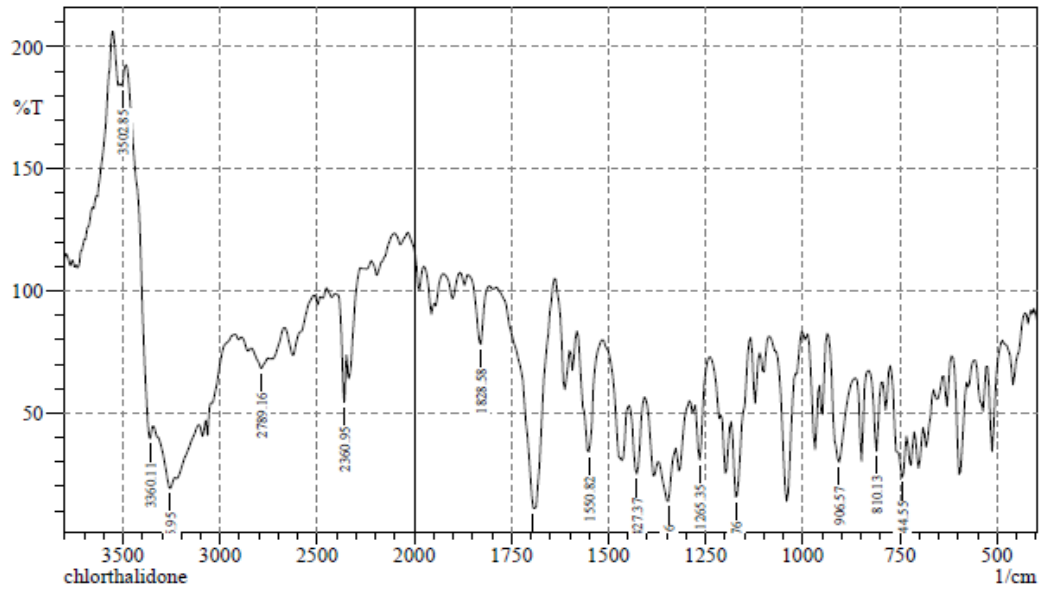

Fig. 8: IR spectrum of Chlorthalidone (pure drug)

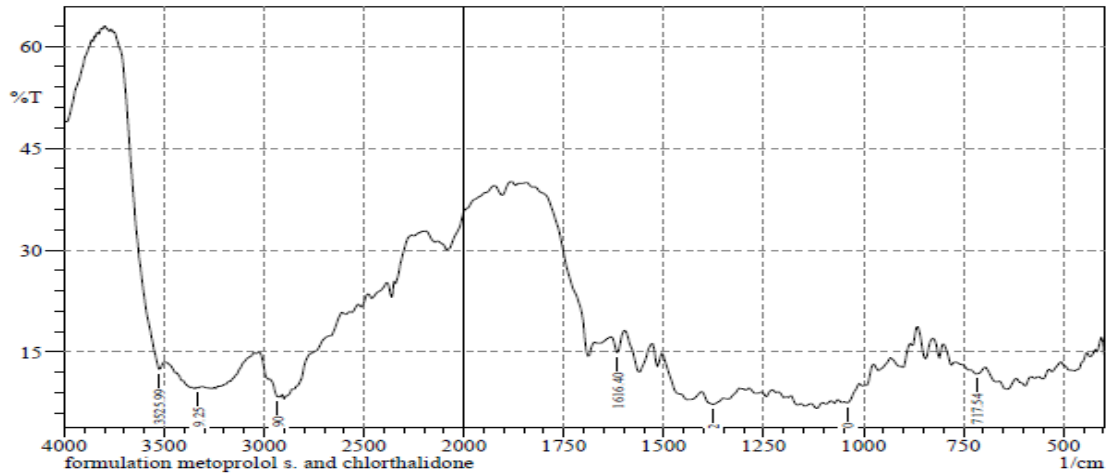

Fig. 9: IR spectra of Metoprolol succinate and Chlorthalidone along with all polymers

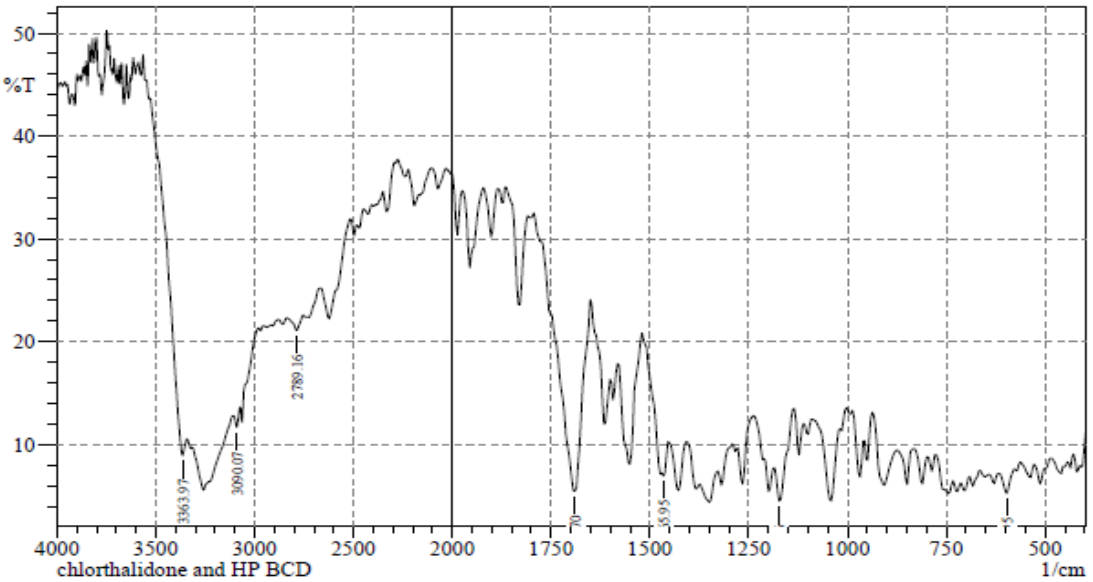

Fig. 10: IR spectra of Chlorthalidone along with hydroxyl propyl ß- cyclodextrin

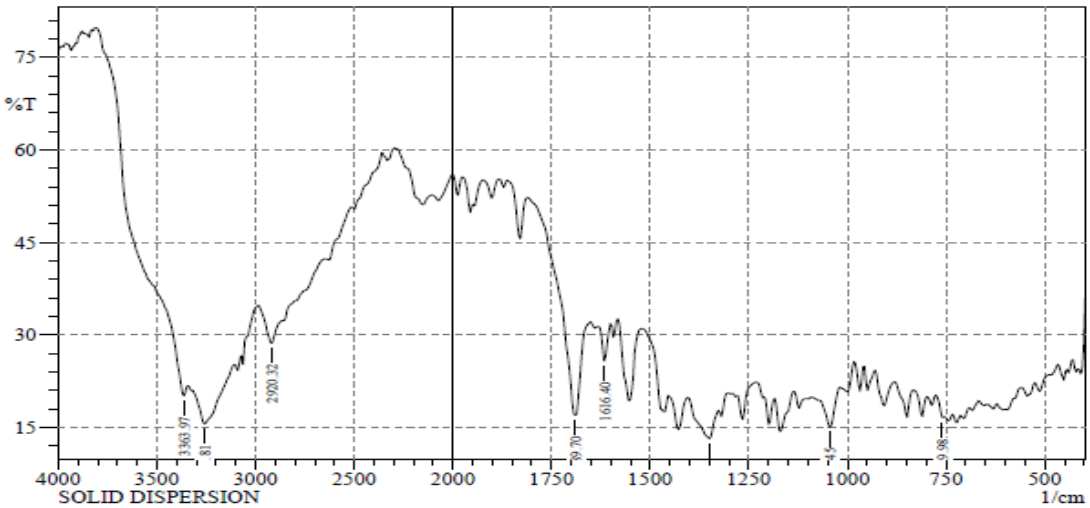

Fig. 11: FT-IR. Spectrum of Chlorthalidone: HP-β-CD Inclusion Complex

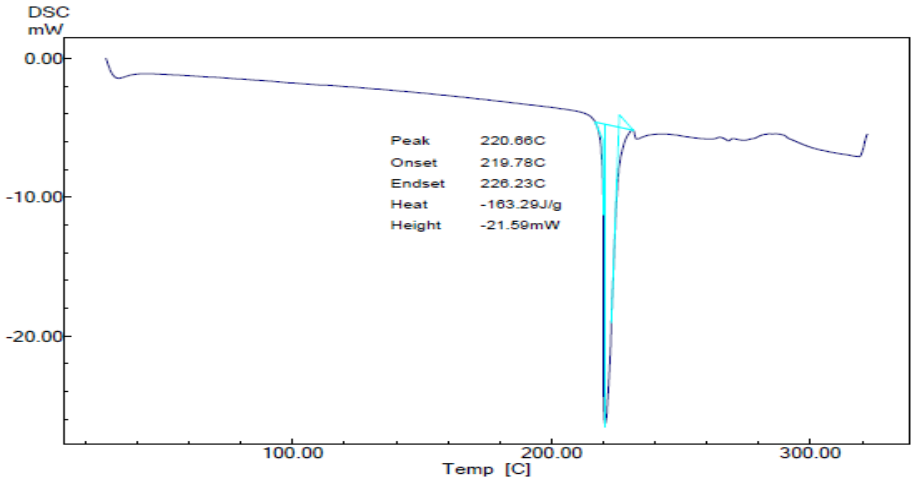

Fig. 12: Thermogram of pure Metoprolol succinate

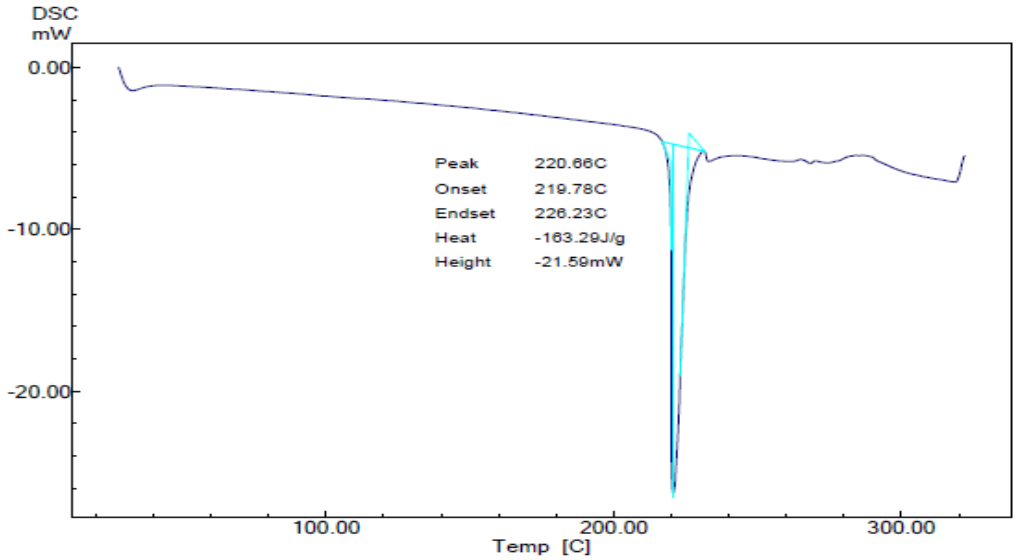

Fig. 13: Thermogram of pure Chlorthalidone

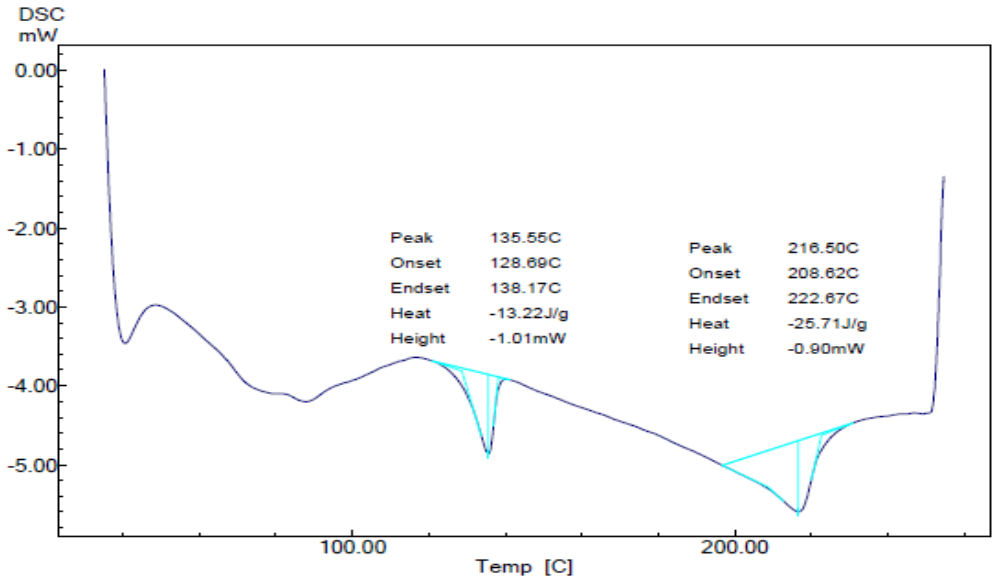

Fig. 14: Thermogram of bilayer tablet formulation

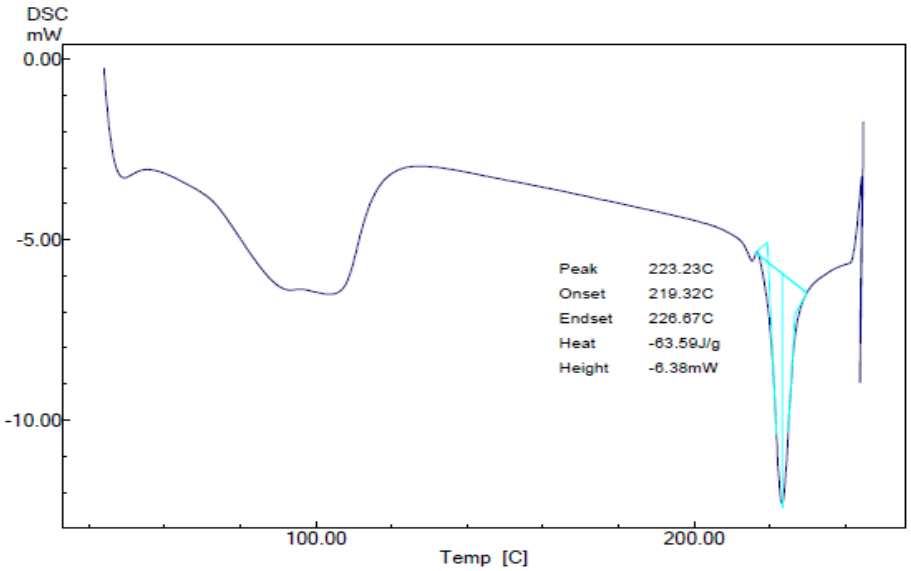

Fig. 15: DSC of Chlorthalidone and HP-β-CD Inclusion Complex

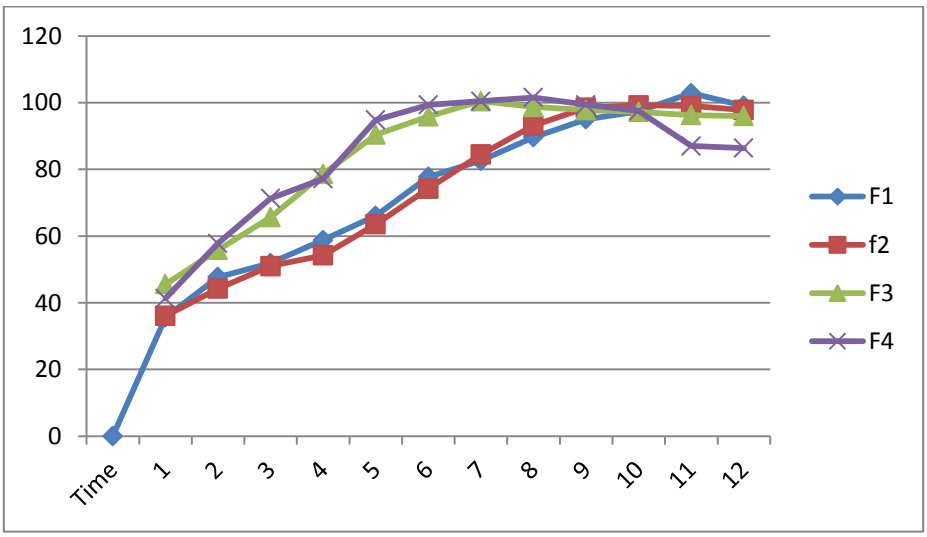

Fig. 16: Comparative in vitro drug dissolution profiles of Metoprolol Succinate SR tablet

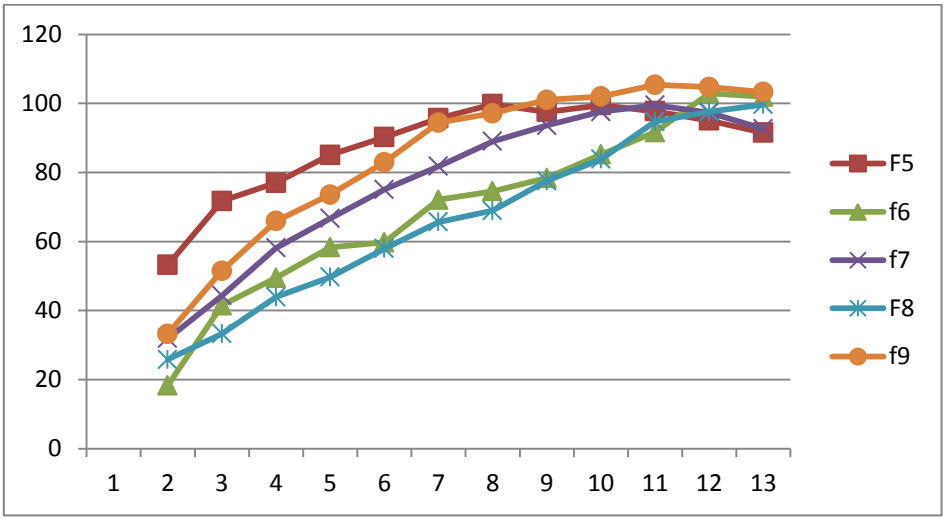

Fig. 17: Comparative in vitro drug dissolution profiles of Metoprolol Succinate SR tablet

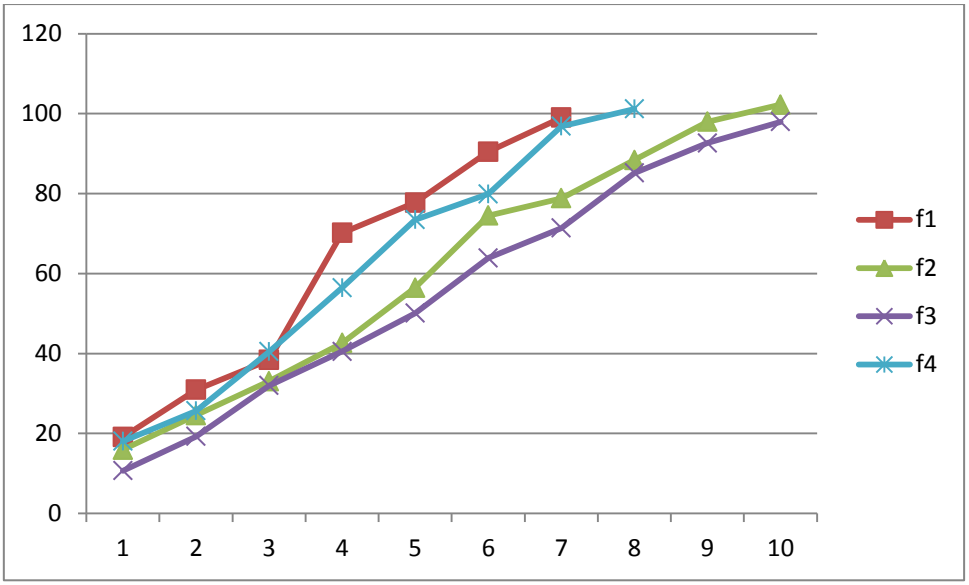

Fig. 18: Comparative in vitro drug dissolution profiles ofChlorthalidone IR tablet (F1-F4)

Table 1: Results of evaluation of *moringa oleifera* gum

Sr. No:	Test	Observation	Inference
1	pH	4.2	Acidic
2	LOD	51.5%	-
3	Tannin	No dark blue color	Absent
4	Starch	No blue or brown color	Absent
5	Sucrose and Fructose	No yellow or pink color	Absent
6	Swelling power	35.2 ml	Passes the test(<40ml)

Table 2: Factorial design calculations for Metoprolol Succinate SR tablet containing HPMC and *Moringa oliefera*

Polymers	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC E15	1	0	-1	-1	-1	1	0	1	0
Moringa oliefera	-1	-1	-1	1	0	0	1	1	0

Table 3: Formula for blend formation and optimization for Metoprolol Succinate SR tablet containing HPMC and *Moringa oliefera*

INGREDIENTS	FORMULATIONS								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol succinate	50	50	50	50	50	50	50	50	50
HPMC E15	60	50	40	40	40	60	50	60	50
Moringa Oliefera	30	30	30	50	40	40	50	50	40
MCC PH102	42.5	52.5	62.5	42.5	52.5	32.5	32.5	22.5	42.5
Talc	10	10	10	10	10	10	10	10	10
Mg.sterate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Starch paste	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
TOTAL	200	200	200	200	200	200	200	200	200

Table 4: Different Ratios Used for Preparation of Inclusion complex of Chlorthalidone

Sr. No.	Carrier	Drug: Carrier Ratio ($^{w}/_{w}$)		
1	Hydroxy propyl ß-cyclodextrin.	1:1	1:3	1:5

Table 5: factorial design calculation

Polymers	F1	F2	F3	F4
Crosspovidone	+1	-1	+1	-1
SSG	+1	-1	-1	+1

Table 6: Formula for blend formation and optimization of Chlorthalidone IR tablet

Ingredients	Formulations			
	F1	F2	F3	F4
Inclusion complex of Chlorthalidone	Equivalent to 12.5 mg	Equivalent to 12.5 mg	Equivalent to 12.5 mg	Equivalent to 12.5 mg
Crosspovidone	10	4	10	4
SSG	10	10	4	4
Magnesium stearate	5	5	5	5
Talc	5	5	5	5
Avicel pH 102	13.75	19.25	19.25	25.75

Table 7: Evaluation of Metoprolol succinate sustained release granules

Formulation code	Bulk density (gm/ml)±S.D	Tapped Density (gm/ml) ±S.D	Angle of Repose(θ) Degrees ±S.D	Hausner's Ratio ±S.D	Carr's Index(%)±S.D
F1	0.472±0.012	0.564±0.026	27.18±0.15	1.194±0.17	16.312±0.13
F2	0.456±0.013	0.567±0.025	29.17±0.18	1.243±0.15	19.576±0.15
F3	0.453±0.012	0.523±0.022	30.01±0.14	1.154±0.18	13.38±0.18
F4	0.448±0.016	0.538±0.026	28.09±0.15	1.200±0.16	16.728±0.14
F5	0.46±0.02	0.565±0.025	30.12±0.16	1.228±0.11	18.584±0.13
F6	0.445±0.03	0.55±0.023	28.9±0.12	1.236±0.22	19.09±0.17
F7	0.464±0.012	0.599±0.026	30.07±0.19	1.290±0.16	22.53±0.16
F8	0.472±0.011	0.587±0.022	24.09±0.13	1.243±0.18	19.59±0.14
F9	0.465±0.013	0.59±0.023	29.15±0.11	1.268±0.21	21.18±0.19

Table 8: Evaluation of Metoprolol succinate sustained release tablet

Formulation code	Thickness (mm)	Hardness ±SD (kg/cm^2)	Weight variation Average weight in mg (% deviation)	Friability (%)	Drug content
F1	3.69±0.07	5.3±0.23	197.03 (1.5%)	0.81±0.23	98.21±0.7
F2	3.58±0.05	5.8±0.21	195 (2.5%)	0.75±0.34	99.12±0.10
F3	3.54±0.04	5.5±0.18	196.8 (1.6%)	0.71±0.25	98.32±0.12
F4	3.56±0.05	5.1±0.26	197 (1.5%)	0.69±0.18	99.25±0.22
F5	3.72±0.08	5.4±0.19	193.5 (3.3%)	0.73±0.22	98.12±0.18
F6	3.64±0.06	5.5±0.17	197.6 (2.2%)	0.85±0.34	99.01±0.15
F7	3.74±0.03	5.2±0.19	195.8 (2.1%)	0.72±0.31	100.04±0.21
F8	3.67±0.08	5.9±0.22	195 (2.5%)	0.70±0.22	99.51±0.22
F9	3.72±0.06	5.7±0.21	197.4 (1.3%)	0.82±0.31	100.12±0.31

Table 9: % Drug release of F1 to F9 formulation containing HPMC E15 and *Moringa oliefera* gum

	Formulation code								
Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	35.64	36.071	45.60	41.33	53.21	18.28	31.87	25.82	33.22
2	47.68	44.23	55.87	57.85	71.70	41.49	44.31	33.26	51.49
3	51.86	51.03	65.64	71.31	77.008	49.48	58.14	43.90	65.93
4	58.76	54.22	78.59	77.18	85.04	58.29	66.64	49.69	73.56
5	66.06	63.56	90.41	94.82	90.20	59.75	75.05	57.93	82.92
6	77.73	74.22	95.88	99.32	95.68	72.10	81.79	65.65	94.41
7	82.57	84.44	100.46	100.43	99.75	74.55	89.00	68.92	97.13
8	89.63	93.159	-	101.55	100.52	78.37	93.61	77.55	101.00
9	95.031	98.50	-	-	-	85.20	97.60	83.81	101.97
10	97.39	99.17	-	-	-	91.64	99.48	94.72	105.36
11	102.825	-	-	-	-	102.87	-	97.58	-
12	-	-	-	-	-	-	-	99.67	-

Table 10: Release kinetics of sustained release tablet

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	0.9838	0.9362	0.707	0.4969	0.6115	0.952	0.9515	0.9905	0.8364
First order	0.9129	0.8598	0.625	0.2432	0.3504	0.9514	0.2304	0.7758	0.4733
Higuchi	0.9873	0.9547	0.8235	0.6364	0.7496	0.9781	0.9923	0.986	0.9295
Hixon Crosswal	0.7866	0.9225	0.4568	0.2184	0.5156	0.6673	0.985	0.9251	0.9262
Krosmeyer peppas	0.9816	0.9571	0.907	0.7931	0.8597	0.9565	0.9949	0.9889	0.9574
Weibul	0.6968	0.6795	0.7273	0.4066	0.472	0.8159	0.6689	0.5329	0.8574

Table 11: Solubility study of solid dispersion Chlorthalidone with PVP K 30

Drug : Polymer ratio	Drug (mg)	PVP K30 (mg)	Absorbance	Concentration (ug/ml)
1:1	50	50	0.142	21.07
1:3	50	150	0.208	30.72
1:5	50	250	0.235	34.67

Table 12: Saturation solubility data for Chlorthalidone and carrier combinations in distilled water

Sr. no	Chlorthalidone: carrier combination	Saturated Solubility (µg/ml)
1	Drug : HP-β-CD (1:1)	45.65
2	Drug : HP-β-CD (1:2)	56.76
3	Drug : HP-β-CD (1:3)	87.13

Table 13: Drug content data for Chlorthalidone and carrier combinations

Sr. No	Chlorthalidone: carrier combination	% Drug content (± SD)
1	Drug : HP-β-CD (1:1)	98.53 ± 0.92
2	Drug : HP-β-CD (1:2)	97.05 ± 0.75
3	Drug : HP-β-CD (1:3)	99.33 ± 1.14

Table 14: Characterization of Powder blend

Formulation code	Bulk density (gm/ml)±S.D	Tapped Density (gm/ml) ±S.D	Angle of Repose(θ) Degrees ±S.D	Hausner's Ratio ±S.D	Carr's Index(%)±S.D
F1	0.463±0.023	0.564±0.026	32.27±0.22	1.218±0.27	17.90±0.13
F2	0.473±0.034	0.567±0.025	29.34±0.12	1.198±0.17	16.57±0.15
F3	0.484±0.012	0.523±0.022	30.01±0.17	1.080±0.21	7.456±0.18
F4	0.435±0.029	0.538±0.026	31.15±0.23	1.236±0.19	19.14±0.14

Table 15: Results of evaluation of Chlorthalidone IR Tablet

Formulation code	Thickness (mm)	Hardness ±SD (kg/cm^2)	Weight variation Average weight in mg(% deviation)	Friability (%)	Disintegration time (min)	Drug content
F1	2.21±0.03	4.1±0.11	148.03 (1.33%)	0.81±0.23	5±0.13	98.21±0.7
F2	2.18±0.06	3.8±0.22	147.8 (1.48%)	0.75±0.34	8±0.23	99.12±0.10
F3	2.24±0.09	4.5±0.18	149.5 (0.33%)	0.71±0.25	5±0.18	98.32±0.12
F4	2.16±0.05	4.1±0.19	148.9 (0.73%)	0.69±0.18	6±0.11	99.25±0.22

Table 16: Results of dissolution study of Chlorthalidone IR tablet

Time (min)	Formulation code			
	F1	F2	F3	F4
5	19.09131	15.93572	10.67641	18.03944
10	30.9382	24.57443	19.25668	25.64383
15	38.40643	33.08283	31.99591	40.49262
20	70.17852	42.64894	40.52768	56.44003
25	77.75778	56.45172	50.09379	73.45099
30	90.49116	74.50869	63.89657	79.89072
35	99.02294	78.83886	71.37648	96.84909
40	-	88.38159	85.16757	101.1734
45	-	97.95354	92.64748	-
50	-	102.237	97.97692	-

CONCLUSION

Combination of natural and synthetic polymer shows the good sustained released action. Due to formation of sustained release tablet of Metoprolol Succinate and Immediate release Chlorthalidone, better patient compliance achieved. Both polymer HPMC E15 and *Moringa oliefera* in high concentration showed good result. Due to solubility enhancement of Chlorthalidone, better bioavaibility is achieved.

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