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FORMULATION AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE TABLETS OF CARVEDILOL

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ABSTRACT

The objective of the present investigation was to design and develop sustained drug delivery system of tablets. Sustained release tablets of Carvedilol was developed using different polymers like HPMC K_4M, Xanthan gum and Eudragit S-100. Sustained tablets of Carvedilol were prepared by wet granulation method. The prepared tablets evaluated in terms of their precompression studies, post compression parameters and *in vitro* study. The results of *in vitro* drug release studies showed that formulation (FCSRT-7) has better control over release of drug (95.78%) when compared to marketed product (90.36%) for 12hrs.

KEY WORDS

Carvedilol, HPMC K4M, Xanthan gum and Eudragit S-100, Wet granulation method and *in vitro* study.

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INTRODUCTION

Oral drug delivery remains the preferred route for administration of various drugs. Solid dosage forms are popular because of ease of administration[1-3], accurate dosage, self-medication, pain evasion and most importantly the patient compliance.

Sustained-release oral delivery systems are de-signed to achieve therapeutically effective concentrations of period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects[4]. Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale-up points of view[1]. Moreover, it has been shown that the suitable combination of more types of polymers as matrix-forming materials enables appropriate modifications of the release characteristics of the drug from the dosage form[5, 6].

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity. Carvedilol beta-adrenergic receptor blocking ability decreases the heart rate, myocardial contractility and myocardial oxygen demand. Carvedilol also decreases systemic vascular resistance via its alpha adrenergic receptor blocking properties. Carvedilol and its metabolites also prevent OH- radical-induced decrease in sarcoplasmic reticulum Ca2+- ATPase activity. Therefore, Carvedilol and its metabolites may be beneficial in chronic heart failure by preventing free radical damage[7].

Its very poor aqueous solubility indicates that its absorption is dissolution rate-limited which results in irregular and delayed absorption. Therefore conventional tablets are required to be administered 3 - 4 times a day. A suitable sustained release dosage form of Carvedilol should provide prolonged action and better compliance by the patient.

MATERIAL AND METHOD

MATERIALS

Carvedilol were obtained as a gift samples from Spectrum Pharma, Hyderabad. HPMC K_4M, Xanthangum and Eudragit S-100 were a Gift sample from Apex Laboratories Pvt.Ltd, Chennai. Magnesium stearate, PVP K-30, Isopropyl alcohol and Talc were obtained as a gift samples from SDFCL, Mumbai. All other chemicals and reagents used were of analytical grade.

drug in the systemic circulation over an extended

METHOD

Preparation of Carvedilol sustained release tablets

Tablets were prepared by wet granulation method. Carvedilol (12.5mg) was mixed with required amount of polymers and other excipients (Table No.1). All the excipients were passed through sieve no.60, mixed and granulated with 10% solution of PVP K-30 in isopropyl alcohol. The wet mass was passed through sieve no.14 and dried at 45^{o}C for 30mints. Dried granules were passed through sieve no.25 and mixed with magnesium stearate and talc[8, 9].

EVALUATION PARAMETERS [9]

Precompression studies of granules

Bulk density

5gms of granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

$$\textbf{Tapped density} = \frac{\textbf{Weight of granules}}{\textbf{Tapped volume of granules}}$$

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal (Table No.2).

$$\theta = \text{Tan}^{-1}(h/r)$$

Where,

θ = Angle of repose,
h = Height of the powder cone,
r = Radius of the powder cone.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density (Table No.3).

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD = Tapped density
BD = Bulk density

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules (Table No.4).

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

Postcompression studies of Carvedilol sustained release tablets

Hardness or Crushing strength Test

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10kg ; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg)[10].

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier calliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight
F - Final weight

Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula (Table No.5),

$$\text{Percentage deviation} = [X - X^{*} / X] \times 100$$

Where,

X - Actual weight of the tablet
X* - Average weight of the tablet

Estimation of Drug Content

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was transferred into 250ml volumetric flask, it was shaken with 150 of distilled water and volume was adjusted to 250ml with water. The solution was filtered, suitable dilutions were made and absorbance was recorded by using U.V. spectrophotometer (Labindia, Hyderabad) at 241nm. The experiment was repeated three times.

Calculation

The amount of Carvedilol present in tablet can be calculated using the formula

$$A_t / A_s \times S_w / 100 \times 100$$

Where,

A_t = Absorbance of sample preparation
A_s = Absorbance of Standard preparation
S_w = weight at Carvedilol working standard (mg)

***In vitro* drug release study**

In vitro release studies were carried out by using USP paddle dissolution test apparatus. 900ml of phosphate buffer (pH 6.8) was taken in the

dissolution vessel and the temperature of the medium was maintained at 37±0.5°C. 100rpm was maintained, 1 ml of sample was withdrawn at predetermined time intervals for 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours. The same volume of the fresh medium was replaced. The samples were analysed at 241nm by using a UV spectrophotometer (Labindia, Hyderabad). The dissolution data obtained were plotted as percentage drug release versus time.

Bioequivalence studies

The bioequivalence study was carried out for 12 hours using USP paddle type dissolution apparatus in phosphate buffer (pH 6.8) at 100 rpms maintaining temperature at 37±0.5^{0}C. A 10ml samples were collected from each vessel at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours and analyzed by UV spectrophotometer at 241nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time.

RESULTS AND DISCUSSION

Preformulation studies

Compatability studies (Fourier Transform Infrared Spectroscopic studies)

The fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated tablets, pure drug and polymers was recorded. The tablets were taken in a KBr pellet using SHIMADZU, 8400s, Japan, FTIR Instrument. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the pure drug and polymers. Then all the functional groups found in the IR spectrum of pure drug and polymers Figure No.1-5.

Precompression studies of granules

Bulk density

The packing properties of the drugs and their formulations widely depend upon bulk density. It has been stated that bulk density values less than 1.2gm/cm^3 indicate good flow and values greater than 1.5 gm/cm^3 indicate poor flow. From the result it can be seen that the bulk density values are less than 1.2gm/cm^3. This indicates good flow characteristics of the granules. Values showed in (Table No.6).

Tapped density

The tapped density was determined by cylindrical method. The tapped density values indicate good flow characteristics of the granules. Values showed Table No.6.

Angle of Repose

Angle of repose can be observed from Table No.6 that the angle of repose for various batches of the granules is found to be less than 40^0, it indicates good flow properties of the granules.

Compressibility Index or Carr's Index

The Carr's Index for various batches of the granules is found to be less than 37; it indicates good flow properties of the sustained release tablets. Values showed Table No.6.

Hausner's Ratio

Hausner's Ratio can be observed from Table No.6 that the Carr's Index for various batches of the sustained release tablets is found to be less than 1.35; it indicates good flow properties of the sustained release tablets.

Postcompression studies of Carvedilol sustained release tablets

Hardness Test

The hardness of the tablet various batches were determined. The various batches of the tablets of hardness values are found within limits and it indicates good strength of the tablets. Values showed Table No.7.

Thickness Test

The sustained release tablets mean thicknesses were almost uniform in the all formulations and were found to be in the range of 4.5mm. Values showed Table No.7.

Friability Test

The sustained release tablets Friability values are found to be less than 1% in all cases and considered to be satisfactory. Values showed Table No.7.

Weight variation test

All this sustained release tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all

tablets was found to be uniform with low standard deviation values. Values showed Table No.7.

Estimation of Drug Content

Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug with the excipients. Values showed Table No.7.

***In vitro* drug release study**

The *in vitro* drug release profile of tablets from each batch (FCSRT-1 to FCSRT-7) was carried in phosphate buffer (pH 6.8) for 12 hrs by using paddle type of device. From the *in vitro* dissolution data, FCSRT-7 formulation was found that the drug release is best and the cumulative % of drug release was 95.78 % respectively, when compared to other formulation (Table No.8 and Figure No.6).

Bioequivalence studies

The promising formulation FCSRT-7 was found by evaluation studies were compared with Marketed product (CARVE 12.5mg), the FCSRT-7 formulation gave 95.78% of the drug release and the Marketed product gave 90.36% of drug release in 12 hours of dissolution study. The formulation FCSRT-7 with 95.78% of drug release has better control over release of drug is compared to marketed product (Table No.9 and Figure No.7).

Table No.1: Formulation of different batches of Carvedilol sustained release tablets (mg/tab)

S.No	Formulations	Drug (Carvedilol)	Polymers			PVP K_{30}	Magnesium stearate	Talc
			HPMC K_4M	Xanthan Gum	Eudragit S-100			
1	FCSRT-1	12.5	52.5	--	--	Q.S	25	10
2	FCSRT-2	12.5	--	52.5	--	Q.S	25	10
3	FCSRT-3	12.5	--	--	52.5	Q.S	25	10
4	FCSRT-4	12.5	26.25	26.25	--	Q.S	25	10
5	FCSRT-5	12.5	--	26.25	26.25	Q.S	25	10
6	FCSRT-6	12.5	26.25	___	26.25	Q.S	25	10
7	FCSRT-7	12.5	17.5	17.5	17.5	Q.S	25	10

Total weight of the tablet = 100mg.

Table No.2: Angle of Repose I.P limits

S.No	Angle of Repose	Powder flow
1	< 25	Excellent
2	25 – 30	Good
3	30 – 40	Passable
4	> 40	Very poor

Table No.3: Carr's Index I.P limits

S.No	Carr's Index	I.P Limits value
1	Excellent	<10
2	Good	11 – 15
3	Fair	16 – 20
4	Possible	21 – 25
5	Poor	26 – 31
6	Very poor	32 – 37
7	Very very poor	>38

Table No.4: Hausner's Ratio I.P Limits

S.No	Hausner's Ratio	I.P Limits value
1	Excellent	1.00 – 1.11
2	Good	1.1 – 1.18
3	Fair	1.19 – 1.25
4	Possible	1.26 -1.34
5	Very poor	1.35 -1.45
6	Very very poor	>1.60

Table No.5: Weight variation test for Tablets

S.No	Average weight of Tablets(mg)	Maximum % difference allowed
1	130 or less	± 10
2	130-324	±7.5
3	More than 324	±5

Table No.6: Precompression studies of granules

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
1	FCSRT-1	0.424	0.465	34.26	8.817	1.096
2	FCSRT-2	0.442	0.483	32.15	8.488	1.092
3	FCSRT-3	0.436	0.472	34.86	7.627	1.082
4	FCSRT-4	0.412	0.456	32.38	9.649	1.106
5	FCSRT-5	0.436	0.472	34.26	7.627	1.082
6	FCSRT-6	0.452	0.483	32.45	6.418	1.068
7	FCSRT-7	0.448	0.494	36.42	9.311	1.102

Table No.7: Postcompression studies of Carvedilol sustained release tablet

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (mm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content (%)
1	FCSRT-1	12.45	4.5	0.531	99.6	95.626
2	FCSRT-2	12.80	4.5	0.669	99.8	95.312
3	FCSRT-3	13.14	4.5	0.672	99.5	95.937
4	FCSRT-4	13.25	4.5	0.404	99.6	96.718
5	FCSRT-5	12.85	4.5	0.739	99.9	95.156
6	FCSRT-6	13.10	4.5	0.534	99.8	94.062
7	FCSRT-7	13.30	4.5	0.743	99.9	96.250

Table No.8: Comparative dissolution study of different formulations with various ratios of Polymers

S.No	Time (hrs)	% of drug release (FCSRT-1)	% of drug release (FCSRT-2)	% of drug release (FCSRT-3)	% of drug release (FCSRT-4)	% of drug release (FCSRT-5)	% of drug release (FCSRT-6)	% of drug release (FCSRT-7)
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	06.23	06.74	07.58	08.64	10.75	11.58	12.46
3	2	12.56	13.24	14.25	15.46	21.52	23.68	27.69
4	3	15.42	16.53	21.64	23.14	31.67	33.87	36.45
5	4	21.48	23.28	27.24	29.36	39.86	41.28	43.54
6	5	28.95	29.84	32.97	34.52	47.64	52.12	56.69
7	6	36.74	37.45	39.46	41.29	56.43	58.07	62.38
8	7	42.68	43.56	46.85	48.64	59.62	62.28	71.56
9	8	48.12	50.32	52.48	54.32	67.23	69.16	78.23
10	9	55.26	57.62	68.27	70.58	74.12	76.43	84.34
11	10	62.05	64.21	73.68	76.08	79.74	81.45	89.68
12	11	69.16	71.64	79.25	81.53	85.39	87.06	92.45
13	12	75.24	78.12	84.56	87.62	90.42	92.36	95.78

Table No.9: Bioequivalence study of Formulation-7 (FCSRT-7) and Marketed Sample (Carves)

S.No	Time (hrs)	% of drug release (FCSRT-1)	Marketed Sample (Carves)
1	0	0.000	0.000
2	1	12.46	08.74
3	2	27.69	15.52
4	3	36.45	24.28
5	4	43.54	32.92
6	5	56.69	40.82
7	6	62.38	48.78
8	7	71.56	55.12
9	8	78.23	62.29
10	9	84.34	70.64
11	10	89.68	77.52
12	11	92.45	83.35
13	12	95.78	90.36

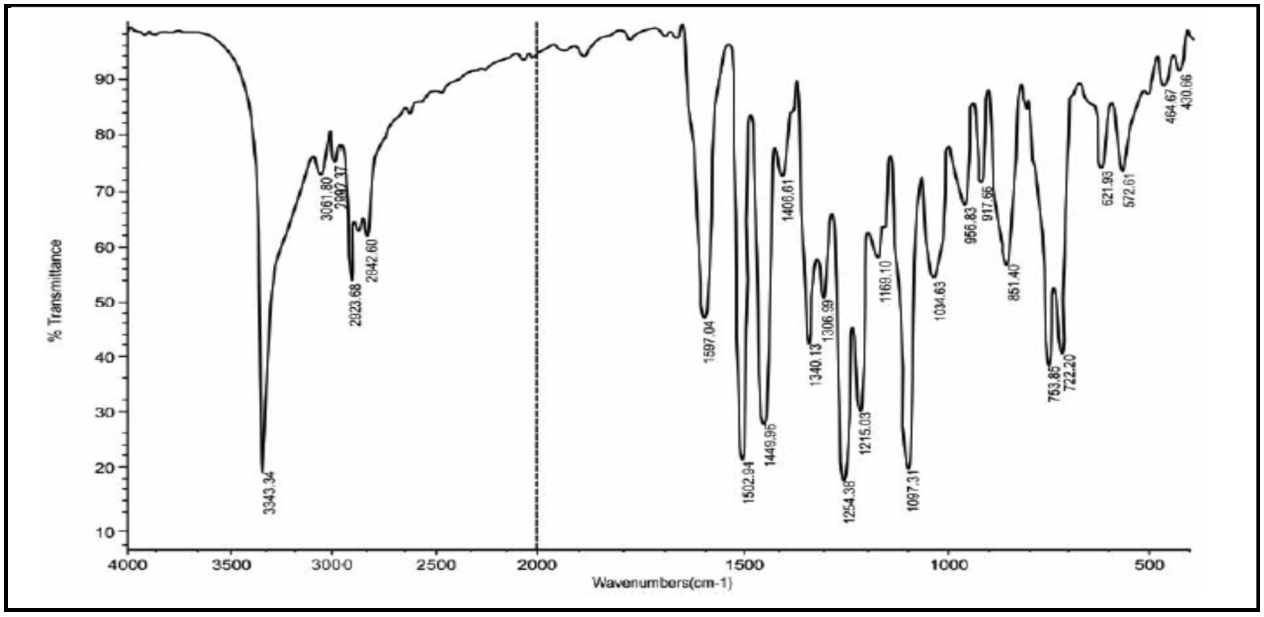

Figure No.1: IR Spectra for Carvedilol

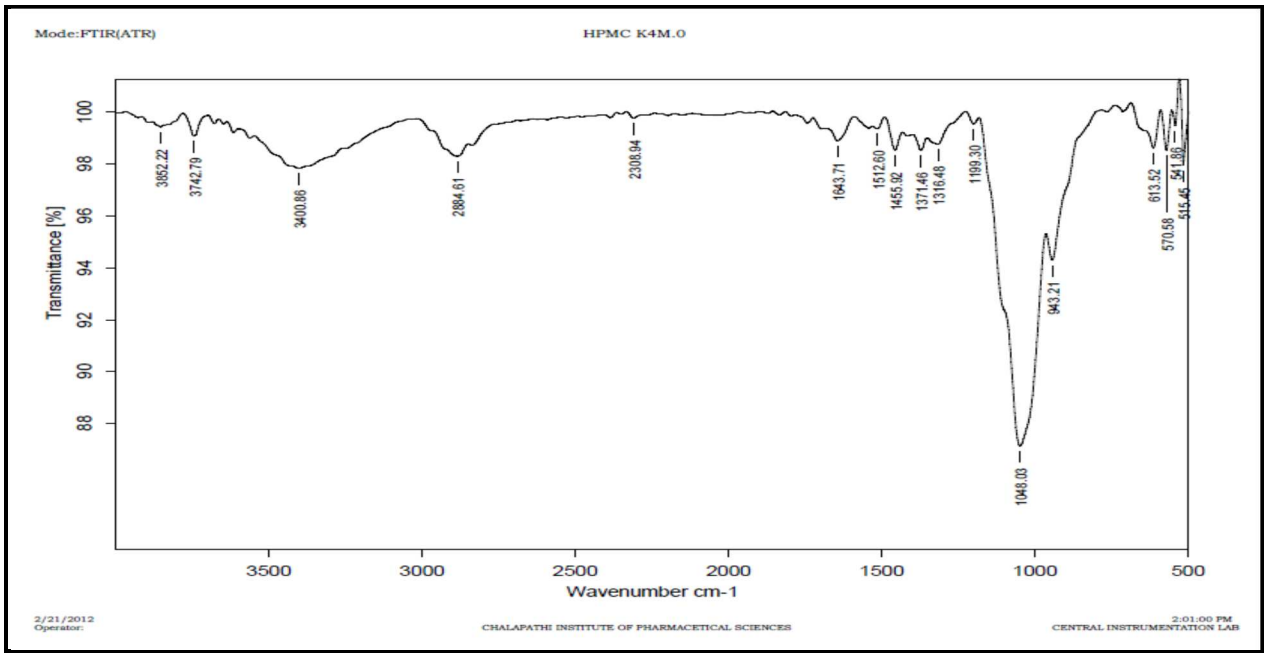

Figure No.2: FTIR spectrum of HPMC K4M

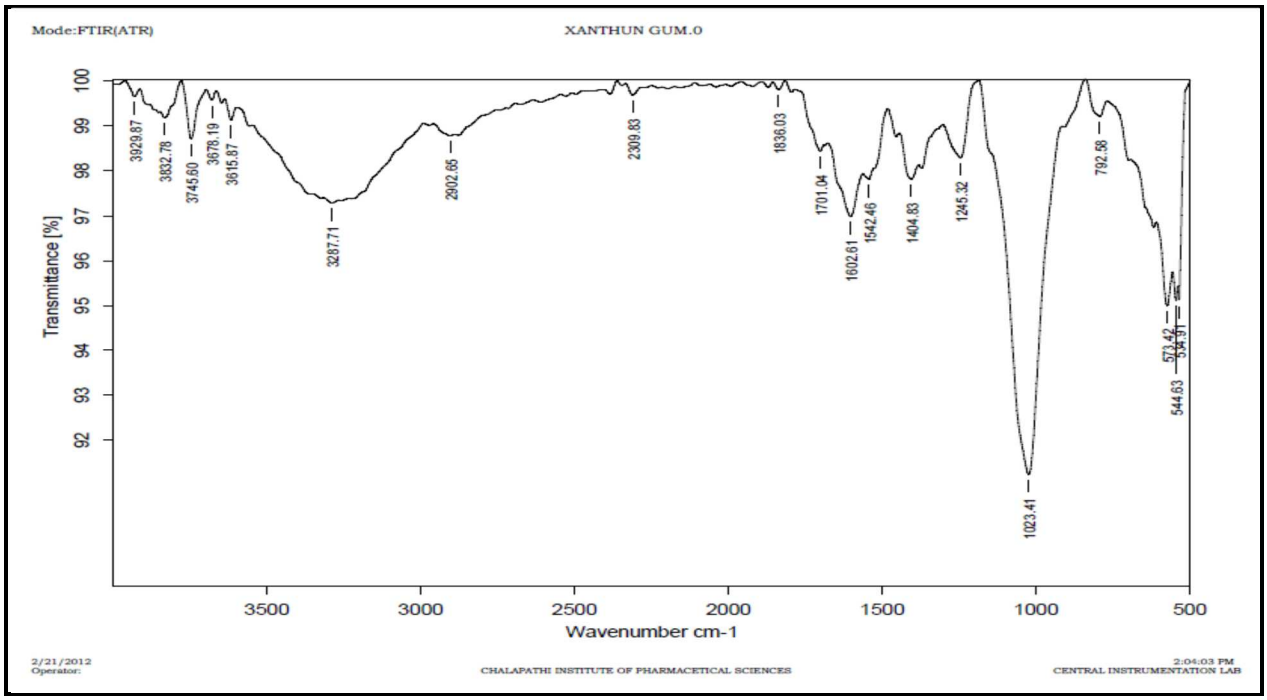

Figure No.3: FTIR spectrum of Xanthan gum

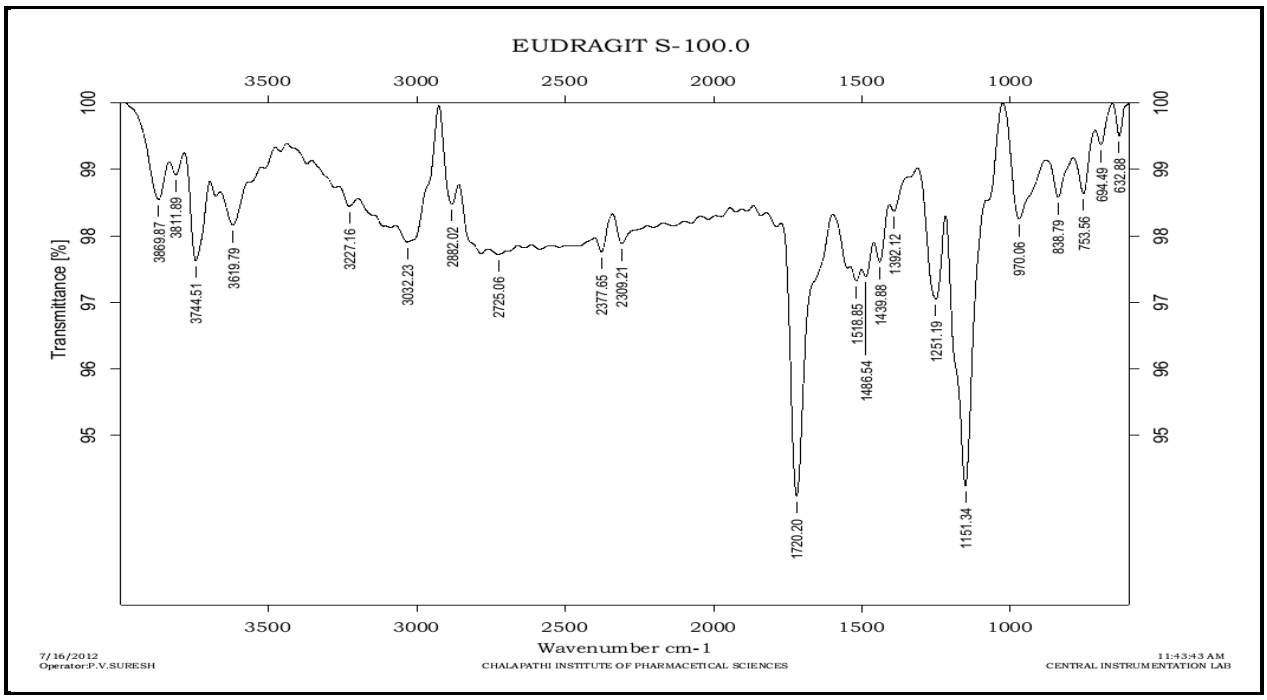

Figure No.4: FTIR spectrum of Eudragit S-100

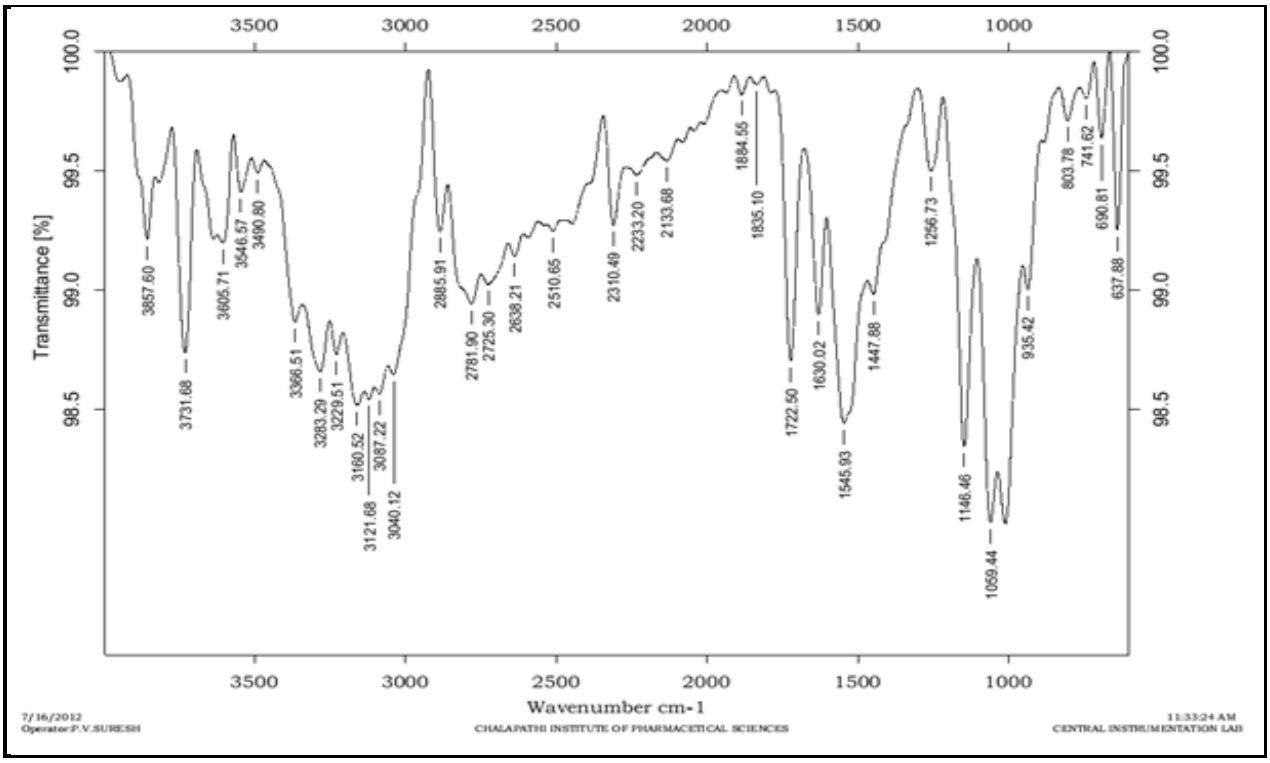

Figure No.5: FTIR spectrum of HPMC K4M + Xanthan gum + Eudragit S-100

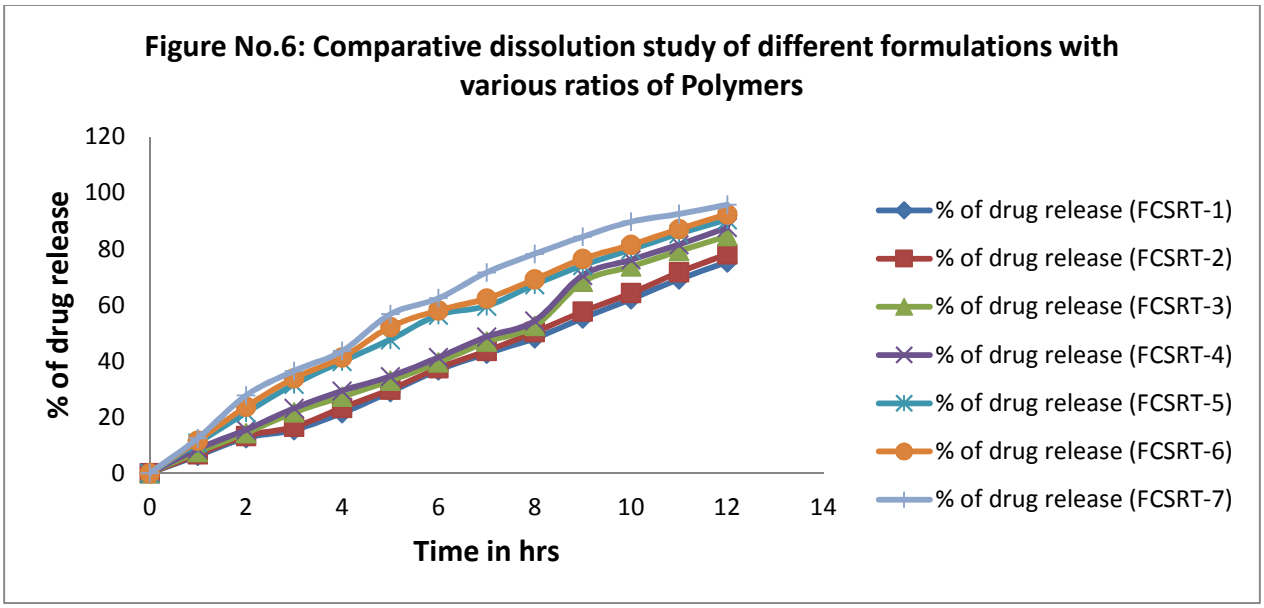

Figure No.6: Comparative dissolution study of different formulations with various ratios of Polymers

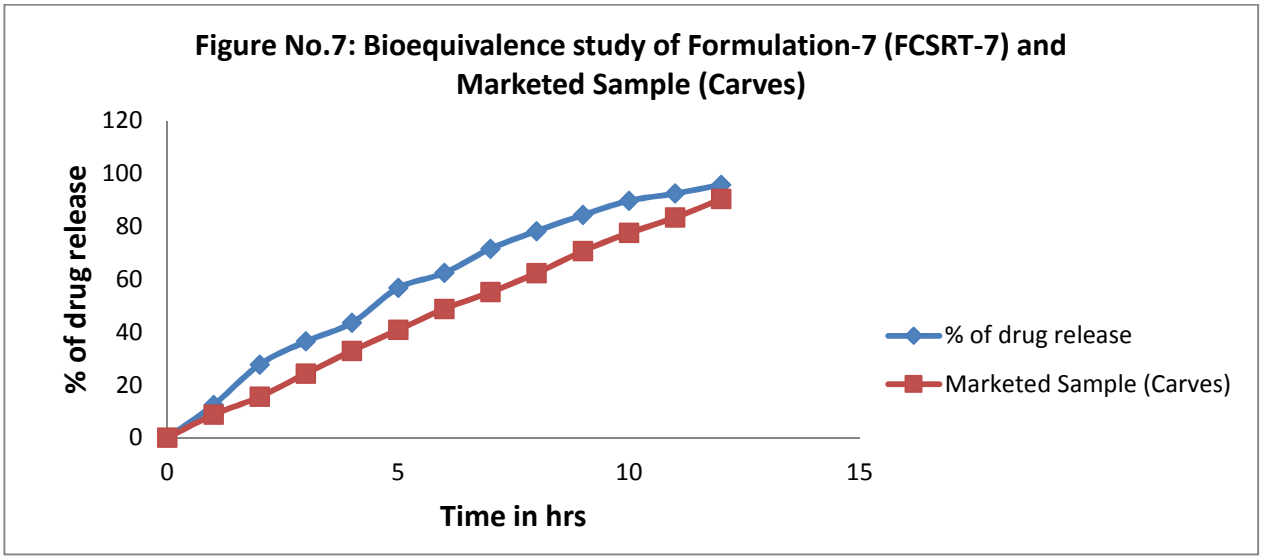

Figure No.7: Bioequivalence study of Formulation-7 (FCSRT-7) and Marketed Sample (Carves)

CONCLUSION

From the above study was concluded that the pre-compression and post-compression studies values are present in within the limits. *In vitro* dissolution studies showed that the formulation FCSRT-7 gave the maximum percentage of drug release (95.78%) within 12 hrs respectively, when compared to other formulation. The FCSRT-7 formulation gave 95.78% of the drug release and the Marketed product gave 90.36% of drug release in 12 hours of dissolution study. The formulation FCSRT-7 with 95.78% of drug release has better control over release of drug is compared to marketed product.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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