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FORMULATION AND EVALUATION OF ATENOLOL SUSTAINED RELEASE TABLETS BY USING NATURAL POLYMERS.

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Abstract:

The aim of present study was to develop sustained release tablet of atenolol by using natural polymers. Physicochemical properties of gum Moringa oleifera was studied like loss on drying, pH,viscocity, Sustained tablet of atenolol was prepared by using gum Moringa oleifera, Gaur Gum, Xanthan Gum in various concentrations by direct compression using 8 mm concave punch. Precompresion parameter was studied. All the observations are within the prescribed limits. Prepared Atenolol tablets were evaluated for post compression parameters which are in acceptable ranges. The drug content of the tablets was found between 98.23-98.75 %.The in-vitro drug releases studies showed that formulation containing lower concentration of polymer had earlier drug release. As concentration of polymer increased, drug release was found to be retarded. F7 showed good result overall as compared to others that is 89.19%. FTIR Studies shows there was no interaction found between any excipient and drug.

Keywords: *Atenolol, Moringa oleifera gum, Guar gum, Xanthan gum, Sustained release tablets.*

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INTRODUCTION:

A common problem associated with conventional therapy is that "dose dumping" or "dose loading" resulting in increased risk of toxicity. Conventional therapy is also associated with high incident of gastro intestinal side effects [1].Sustained and drug delivery systems are designed to achieve therapeutically effective concentration of drug in systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and incidence of adverse side effects. Sustained and controlled drug delivery systems significantly improve therapeutic efficiency of drugs [2].

Drug-release-retarding polymers are the key performers in such system. Most of researchers used synthetic polymers for sustained drug delivery but they individually show specific limitations such as toxicity or expensiveness of polymer. Natural polymer such as resins, polysaccharides and gums have been extensively used for drug delivery system because they are readily available, cost effective, eco-friendly, capable of multitude of chemical modification, potentially degradable and compatible due to natural origin. Since wide range of synthetic, semi-synthetic and combinations of polymers have certain advantages as well as own limitations, therefore, it is primary requirement to investigate new polymeric material for sustained drug delivery system. From the literature survey it reveals that not a single work was carried out by using Moringa oliefera, Gaur gum and Xanthan gum in combination. [3,4]

Atenolol, a β-blocker, is prescribed widely in diverse cardiovascular diseases, eg. Hypertension, angina pectoris, arrhythmias, and myocardial infarction. Atenolol is an acid soluble, this property of Atenolol results in rapid drug absorption and clearance, causing large and undesirable fluctuation of drug plasma concentration which requires frequent oral administration for adequate treatment. Therefore a need to develop a method for administrating Atenolol in an oral dosage form once or twice daily in the form extended release tablet. [5]

MATERIALS AND METHODS:

Atenolol was supplied as a Kind gift sample by Kopran ltd., Mahad, India. Moringa oleifera gum was isolated in laboratory, Guar gum, Xanthan gum; Magnesium stearate and Talc were provided by T.V.E.S's H.L.M.C. College of Pharmacy, Faizpur.

Method

Collection, isolation and Authentication of Moringa oleifera gum:

Collection of gum:

The raw materials were collected from the Satpuda region of Pal, Tal: Raver, Dist.: Jalgaon [Maharashtra].

Isolation:

The Moringa oleifera gum was collected from trees [injured site]. It was dried, ground, and passed through sieve no 80 dried gum [10 g] was stirred in distilled water [250 ml] for 6- 8 hrs at room temperature. The supernatant was obtained by centrifugation. The residue was washed with water and the washings were added to separate supernatant. The procedure was repeated four more times. Finally the supernatant was made up to 500 ml and treated with twice the volume of acetone by continuous stirring. The precipitated material was washed with distilled water and dried at 50-60°C. [6]

Physicochemical evaluation of Moringa oleifera gum:

Loss on drying:

The method adopted was that specified in the B.P 2004 for acacia. 1.0 g of the sample was transfer 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

Total ash and acid insoluble ash determination:

Ash content was estimated by the measurement of the residue left after combustion in a furnace at 450°C. The ash obtain from the determination of the ash was boiled with 25 ml of 2M hydrochloric acid solution for 5 minutes and the insoluble matter was filtered and washed with hot water and ignited and the subsequent weight was determined. The percent acid insoluble ash was calculated

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.

Viscosity:

The viscosity was carried out using preparing 1% solution of gum in distilled water. The viscosity was measured using Brookfield viscosity meter.

Drug–Excipient Compatibility Study:

Infrared Spectroscopy:

Drug excipient compatibility testing was performed by mixing drug with polymer in equal proportion then, mixture was kept under accelerated stability condition [i.e. 40ºC and 75±5% RH] for a period of 21 days in a glass vial. It was hermetically sealed with rubber stopper using molten carnauba wax. Same mixture under control condition [i.e. 5% H_2O] was kept. IR spectrum was noted for mixture after 21 days. [Stuart B, *et al*. 1996] The IR spectra of previously dried samples were recorded by potassium bromide dispersion technique. 2-3 mg of sample of solid dispersions was mixed with previously dried IR grade potassium bromide and kept in sample cell, the cell was then fitted on sample holder, spectra were recorded with FTIR instrument and the spectral analysis was done.[7-10]

Preparation of Atenolol Tablet

The matrix tablets containing 50 mg Atenolol were formulated with different proportions of natural gum polymer. Atenolol and all other ingredients were passed through sieve no 60.separately and mixed homogeneously. The powder was lubricated with a mixture of talc and magnesium stearate. Finally the lubricated powders were compressed into tablets containing 50 mg Atenolol using 8 mm concave punch.

Table 1: Preliminary Trial Batches for Selection of Excipients used in Formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Atenolol	50	50	50	50	50	50	50	50	50	50	50	50	50
MoringaGum	60	50	40	70	80	70	80	50	40	60	60	60	60
Gaur gum	60	60	60	60	60	50	40	70	80	50	40	70	40
Xanthan gum	60	70	80	50	40	60	60	60	60	70	80	50	80
Talc	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Mg. stearate	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6

Pre-compression Parameters of Drug Polymeric Blend.

Excipients, polymers and drug were characterized for their physical properties such as angle of repose, density, compressibility, Hausner's ratio.

Evaluation of Prepared Tablets:

General appearance:

The general appearance of a tablet, its visual identity and over all "elegance" is essentialfor consumer acceptance, Including tablet's size, shape, surface texture, consistency and legibility of any identifying marking [11].

Tablet thickness and diameter:

Tablet thickness should be controlled within 5% or less of a standard value. Any variation in tablet thickness should not be apparent to customer. In addition, it is important to control thickness to facilitate packaging. Difficulties may be encountered in the use of unit dose and other type of packaging equipment if the volume of the material being packed is not consistent. The crown thickness of individual tablets is measured with Vernier Caliper. The crown thickness of individual tablets is also determined for the purpose of determining the density of tablet compacts. [12].

Hardness

Hardness of the tablet is determined using Monsanto hardness tester. The tablet to be tested is placed between the spindle and anvil and pressure is applied by turning the knurled knob just sufficiently to hold the tablet in position. The reading of pointer on scale is then adjusted to zero. The pressure is now increased as uniformly as possible until tablet breaks. The pointer now reads the pressure required to break the tablet.

Weight variation test:

Twenty tablets were accurately weighted and an average weight was calculated. Not more than two individual weights deviate from the average weight by the percentage deviation. [13]

Determination of drug content:

Drug content from the tablet was determined by taking tablets from each formulation. Twenty tablets from each formulation were accurately weighed and powdered. Powder equivalent to 50mg of the drug was weighed and transferred into a volumetric flask using 100ml of 0.1N HCL. A suitable volume of filtrate was diluted with a sufficient of 0.1N HCL to produce a solution containing 10mcg of Atenolol. The absorbance was measured at 229nm.

Swelling index

For each formulation, one tablet was weighed and placed in a breaker containing 200ml of 0.1 N HCl.[13] After each hour the tablet was removed from breaker and weighed again up to 8 hours. The percentage weight gain by the tablet was calculated by the formula

Swelling Index [S.I] = $\{[W_t-W_o]/W_o\}$ x 100

Where, S.I. = Swelling index

W_o = Weight of tablet before immersion

W_t = Weight of tablet at time

***In-vitro* dissolution study**

In-vitro release of Atenolol from tablet was carried out using the USP dissolution test apparatus [Type-II]. Dissolution media used was 900 ml of 0.1 N HCI [pH 1.2] maintained at 37 ± 0.5°C and stirred at 50 rpm. At predetermined time intervals, 10 ml of sample was withdrawn and replaced with equal amount of 0.1 N HCI [pH 1.2]. The collected samples were filtered and suitably diluted with 0.1 N HCI and analysed spectrophotometrically at 271 nm to determine the amount of drug released in the dissolution medium.[15]

Accelerated stability studies of optimize formulation batch.

Optimized batch was kept in environmental stability chamber [Remi Lab, Mumbai] for accelerated stability condition at 40ºC temperature and 75 ± 5 % relative humidity for a period of 3 months. The samples were withdrawn at 1, 2, and 3 months interval and evaluated for physical parameters, drug content, in-vitro drug release [16].

RESULT AND DISCUSSION:

Physicochemical studies of Moringa oleifera gum.

Evaluation of Moringa oleifera gum was carried out on various physicochemical parameters such as Micrometric properties, Angle of repose was found to be 22.50±11 °, Bulk density was found to be 0.76 ±0.08, Tapped density was found to be 0.86 ±0.02, Carr's Index was found to be 11.6 ±0.01 which signify the good flow property of gum, Hausner's Ratio was found to be 1.13 ±0.01and Viscosity of gum was measured by using 2% gum concentration and was found to be 900cps. The pH

of gum was found 6.8.total ash value was found to be 6%.

FTIR Studies

The IR spectrum did not show presence of any additional peaks for new functional groups indicating no interaction between Atenolol and polymers used in formulations.

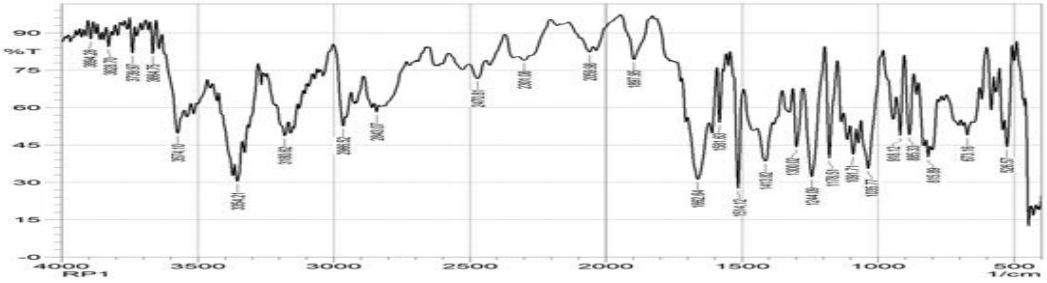

Fig 1: FTIR Spectrum of pure Atenolol

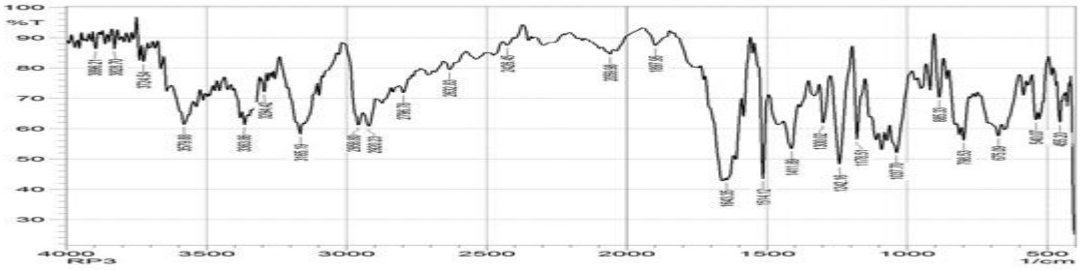

Fig 2: FT-IR spectrum of Atenolol and Moringa oleifera gum

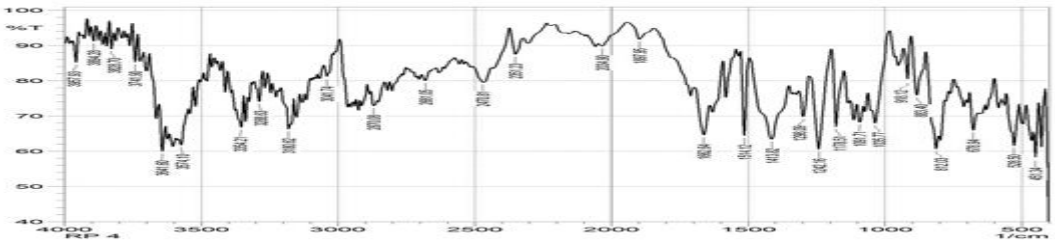

Fig 3: FT-IR spectrum of Atenolol and Guar gum

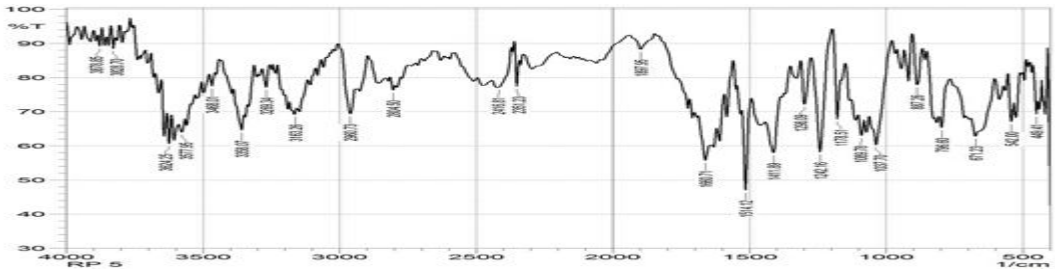

Fig No.:4 FT-IR spectrum of Atenolol and Xanthan gum.

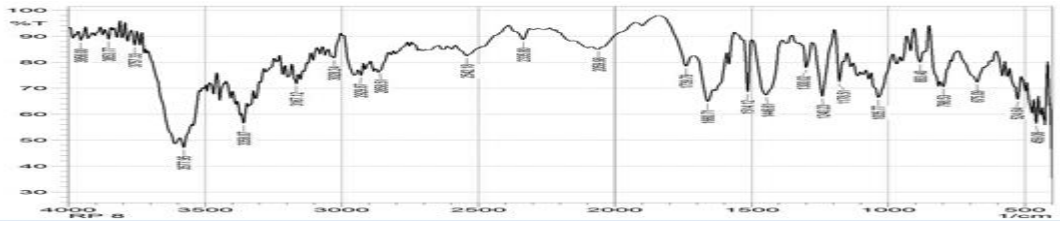

Fig 5: FT-IR spectrum of Physical Mixture.

Table 2: Evaluation of pre-compressional parameters of tablet blends

Batch	Bulk Density	Tapped density	Carr's Index	Hausner's ratio	Angle of repose
F1	0.426±0.016	0.515±0.039	16.69±0.75	1.20±0.01	20.12±0.18
F2	0.424±0.014	0.510±0.045	16.86±0.69	1.21±0.03	23.78±0.26
F3	0.441±0.008	0.525±0.031	16.00±0.56	1.19±0.04	22.95±0.48
F4	0.459±0.017	0.545±0.027	15.77±0.47	1.18±0.02	22.45±0.38
F5	0.461±0.026	0.565±0.023	18.40±0.76	1.22±0.004	25.60±0.32
F6	0.456±0.019	0.543±0.037	16.02±0.64	1.19±0.14	24.86±0.44
F7	0.474±0.042	0.554±0.041	14.44±0.65	1.16±0.08	25.78±0.32
F8	0.423±0.010	0.515±0.025	17.86±0.49	1.21±0.07	21.46±0.34
F9	0.435±0.042	0.526±0.021	17.30±0.46	1.20±0.11	23.25±0.53
F10	0.437±0.015	0.534±0.034	18.16±0.57	1.22±0.04	20.81±0.41
F11	0.492±0.038	0.585±0.042	15.89±0.36	1.18±0.06	21.77±0.34
F12	0.465±0.026	0.523±0.034	11.08±0.44	1.12±0.05	26.20±0.32
F13	0.478±0.013	0.561±0.033	14.79±0.56	1.17±0.02	25.41±0.43

The powder mixtures for all batches [Table No.2] were evaluated for bulk density which ranged from 0.423-0.492[g/ml], tapped density ranged from 0.510-0.585 [g/ml], Angle of repose ranged from 20.12-26.20º, Carr's index ranged from 11.08-18.40 and Hausner's ratio ranged from 1.12-1.22. All these results indicated that, the powder mixture possess satisfactory flow and compressibility properties.

Evaluation of post-compressional parameters of formulated Tablets

The prepared formulation were evaluate for physical characteristics like thickness,hardness , friability, weight uniformity and uniformity of content All the physical parameter of sustain release matrix tablet were within pharmacopoeial limits. Thickness of tablet each formulation measured and found in the range from 3.85-3.93. Hardness of tablet each formulation was measured and found in the range from 5.0-5.6. %weight loss of tablet of each formulation was measured and found to be in the range of 0.65-0.78 which was under acceptable limits. The tablets from each batch showed uniformity of content in the range of 98.23-98.75 % [Table No.3].

Table 3: Evaluation of post-compressional parameters of formulated Tablets

Batch	Thickness [mm]	Hardness [Kg/cm²]	Average weight	Friability [%]	Content Uniformity
F1	3.21±0.43	5.2±0.06	235±0.37	0.58±0.02	98.67±0.26
F2	3.11±0.52	5.0±0.02	236±0.34	0.62±0.01	98.64±0.56
F3	3.12±0.63	5.2±0.11	233±0.26	0.56±0.08	98.23±0.83
F4	3.11±0.71	5.2±0.14	234±0.16	0.52±0.03	98.46±0.63
F5	3.09±0.32	5.6±0.11	234±0.16	0.57±0.04	98.56±0.94
F6	3.23±0.49	5.4±0.13	236±0.48	0.59±0.02	98.51±0.61
F7	3.15±0.21	5.2±0.11	235±0.49	0.48±0.03	98.82±0.79
F8	3.18±0.18	5.0±0.25	234±0.12	0.52±0.01	98.60±0.82
F9	3.17±0.16	5.2±0.41	237±0.21	0.64±0.05	98.22±0.53
F10	3.13±0.11	5.4±0.27	233±0.26	0.61±0.06	98.45±0.64
F11	3.21±0.35	5.6±0.11	234±0.47	0.49±0.04	98.44±0.67
F12	3.24±0.09	5.6±0.09	235±0.41	0.61±0.02	98.56±0.59
F13	3.18±0.12	5.0±0.02	236±0.12	0.54±0.03	98.76±0.73

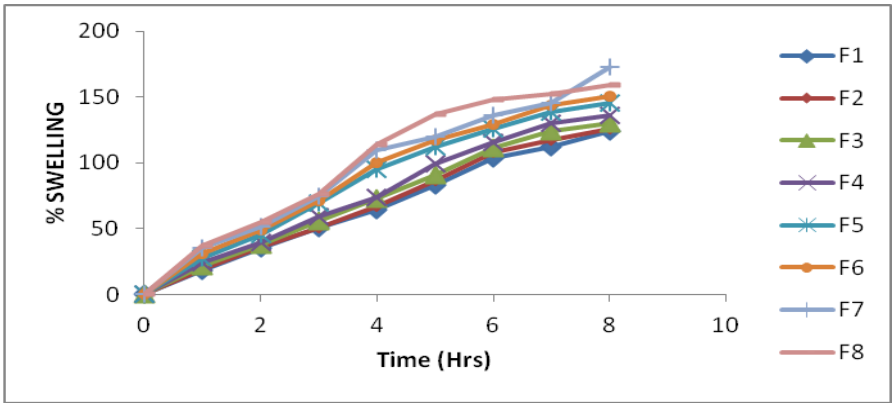

Fig 6: Swelling Index of Batches F1-F8

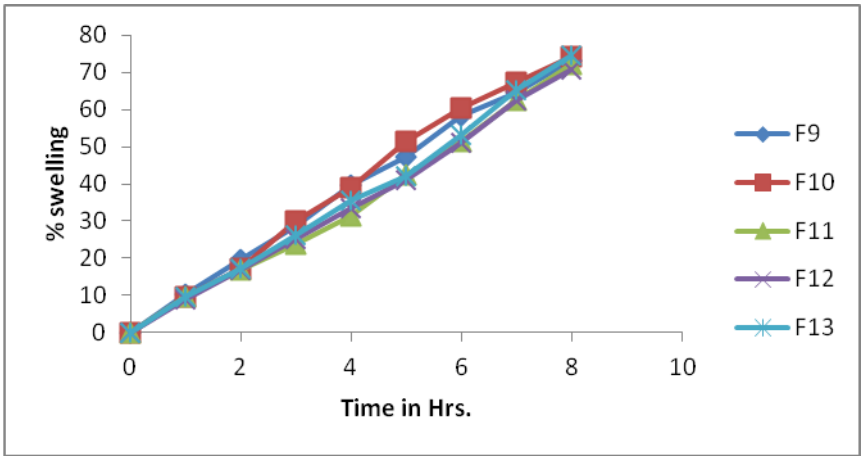

Fig 7: Swelling Index of Batches F9-F13.

Swelling Index studies

The matrices % swelling index increases at the beginning attains a maximum and then declines. From the Figure6, 7 showed maximum swelling due to presence of hydrophilic swellable polymer. It showed that there was a gradual increase in swelling index seen in all formulations up to 8 hours.

***In-vitro* drug release study**

The *in-vitro* drug release study showed that formulation containing lower concentration of polymer had earlier drug release. As concentration of polymer increased, drug release was found to be retarded. F7 showed good result overall as compared to others that is 89.19%. [Fig no 6&7].

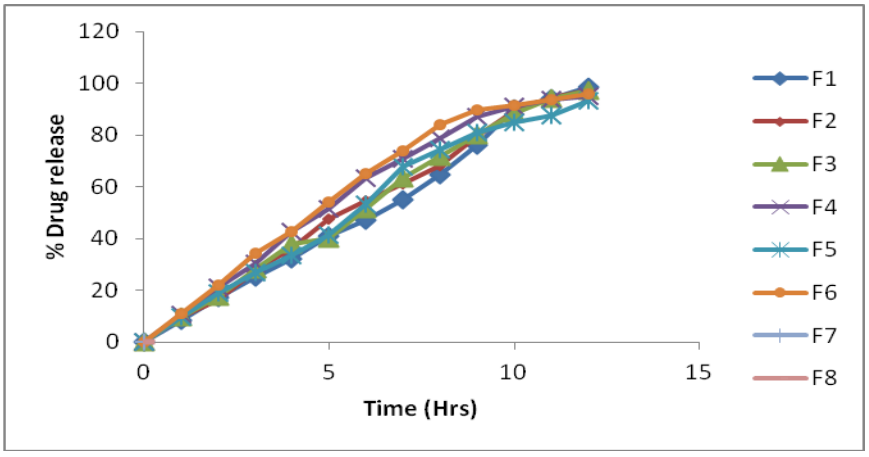

Fig 8: % drug release of F1-F8

Table 4: Comparison of Physical Parameters and Dissolution Profile for Stability Study

Parameters	0	15	30	45	60
Color	No Change	No Change	No Change	No Change	No Change
Hardness	5.2	5.2	5.2	5.2	5.4
Friability	0.48%	0.49%	0.49%	0.51%	0.52%
Con. Uni.	98.82%	98.74%	98.65%	98.43%	97.82%
% Release	89.19%	89.26%	89.42%	89.17%	89.31%

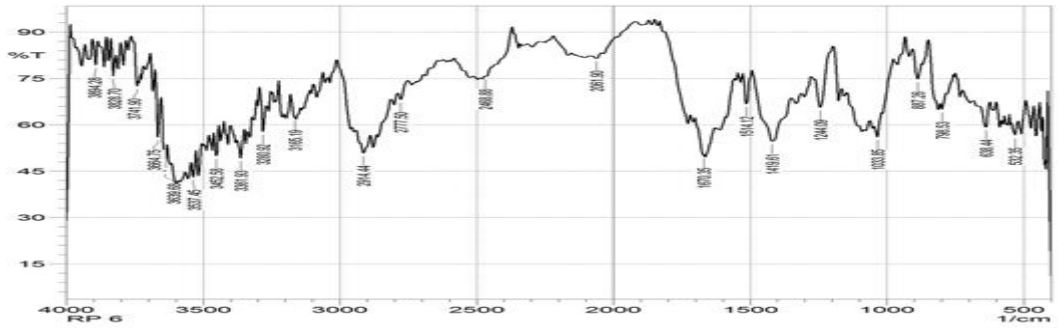

Fig 9: IR Spectrum of Trial Batch 60 after stability study.

Stability Study

F7 was subjected to Accelerated stability studies as per Stability Testing for New Dosage Forms Q1c. Batch F7 was subjected for stability study. All Parameters were given in table No 4. There was no significant change in the parameter after 60 days stability study. Stability of formulation F7 was also confirmed by IR spectroscopic study as shown in Fig No.9. From the IR spectra of Formulation F7 it was clears that the formulation was stable.

CONCLUSION:

The entire above objective were successfully studied and confirmed that matrix tablet of Atenolol containing Moringa oleifera, Guar and Xanthan gum F7 is suitable for preparation of sustained release tablet. Hence study demonstrated that Moringa oleifera, Guar and Xanthan gum can be used as a matrix for preparation of once daily formulation of Atenolol. Hence it can be concluded that use of combination matrices offers a useful means of formulating sustained release dosage forms for a sparingly water soluble drug like Atenolol.

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