Research Article

Development and Evaluation of Gastroretentive Floating Drug Delivery System of Atenolol

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ABSTRACT

Atenolol, an antihypertensive drug, has poor bioavailability (40-50%) and has has low elimination half life(6 hr). Atenolol is mainly absorbed in the stomach. The floating tablets of atenolol were prepared to increase the gastric retention, extend the drug release and to improve the bioavailability of the drug. The floating tablets were formulated using HPMC 100 cps, sodium alginate, carbopol 940 and guar gum as the polymers. The tablets were prepared by direct compression method. The formulated tablets were evaluated for the quality control tests: weight variation, hardness, friability, swelling index, floating lag time and total floating time. The in vitro release of the tablets was evaluated in 0.1N HCl (pH 1.2).The floating tablets extended the drug release up to 8 hrs. The drug-polymer interaction was evaluated by fourier transform infrared spectroscopy(FTIR).The drug release from the optimized formulation followed first order kinetics(regression coefficient,r^2value =0.988) and the Higuchi equation (r^2=0.996).The n value(0.260)calculated for the optimized formulation revealed that the drug release follows fickian diffusion. The similarity factor calculated for the batch F8(optimized formulation) was 70.74%, and its dissolution profile was similar to the dissolution profile of the branded extended release tablet. The FTIR studies indicated the absence of the drug-polymer interaction in the optimized formulation.

Keywords: Atenolol, Gastroretentive , Floating tablets, Polymers, Dissolution.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process.It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS). GRDFs extend significantly the period of time over which the drugs may be released[1,2]. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as – extended release dosage forms with prolonged residence time in stomach are highly desirable for drugs: that are locally active in the stomach, that have an absorption window in the stomach or in the upper small intestine, that are unstable in the intestinal or colonic environment, have low solubility at high pH values. Various approaches have been pursued to increase the retention of an oral dosage form in the stomach[3,4]. These systems include: Floating systems, bioadhesive systems, swelling and expanding systems, high density systems. Floating Drug Delivery System (FDDS) has a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate[5-7]. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of

the drug, the residual system is emptied from the stomach. This, results in an increase in the GRT and a better control of the fluctuations in the plasma drug concentration[8-10].

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are effervescent system and non-effervescent system[11-14].Effervescent systems include use of gas generating agents, carbonates (e.g. sodium bicarbonate) and organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid[15,16].The non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids (HPMC), polysaccharides and matrix forming material such as Polycarbonate, Polyacrylate, Polymethacrylate, Polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol. To achieve gastro retention, the dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms. It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease.

Atenolol,the β1blocker[17,18] is a widely used antihypertensive drug, it has low elimination half life:6 hrs. Atenolol is well absorbed from the gastrointestinal tract ,however the drug is subjected to first pass metabolism and its oral bioavailability is 40-50%.Atenolol is mainly absorbed in the stomach than in the lower gastrointestinal tract. Hence, it is ideally suited for the gastroretentive floating tablets. The objective of the present investigation is to formulate floating tablets, to increase the gastric retention, extend the drug release and to improve its oral bioavailabity. The floating tablets were prepared using different polymers: Guargum, Sodium alginate, HPMC 100cps and Carbopol 940.

MATERIALS AND METHODS

Atenolol was a gift sample from Dr Reddys Labs, Hyderabad. Sodium alginate, guar gum, HPMC 100 cps, Carbopol 940, lactose, dicalcium phosphate and sodium bicarbonate were procured from S.D Fine Chem Ltd, Mumbai.

ESTIMATION OF ATENOLOL

A spectrophotometric method based on the measurement of absorbance at 275 nm in 0.1N HCl was used in the present study for the estimation of Atenolol.The 100mg of Atenolol pure drug was dissolved in 100ml of water(stock solution).The 10 ml of the solution was taken and the volume was adjusted up to 100ml with water (100µg/ml) The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 2, 4, 8, 12, 16, 20,24,30,50 and 100µg/ml of Atenolol**.**The absorbance of the above dilutions was measured at 275 nm by using UV-Spectrophotometer(Lab India) taking 0.1N HCl as the blank. Then, a graph was plotted by taking concentration on x-axis and absorbance on y-axis, which gave a straight line (Fig.1).

PREPARATION OF TABLETS

All the formulations were prepared by direct compression. The composition of the different formulations is given in Table1.The tablets were prepared as per the procedure given below and the aim is to prolong the release of Atenolol tablet. Atenolol and all other ingredients were individually passed through sieve no ≠ 60.All the ingredients were mixed thoroughly for 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using the direct compression method.

EVALUATION OF TABLETS

The formulated tablets were evaluated for the following physicochemical characteristics:

General appearance
The formulated tablets were assessed for its general appearance and observations were made for shape, color, texture and odor.

Hardness test
Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) 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 turning 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.

Weight Variation
The 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

Friability test
The 20 previously weighed tablets were placed in the apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula:Percentage friability = (initial weight - final weight) / initial weight × 100.

Drug content
The 10 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Atenolol was transferred in to a 100 ml volumetric flask and the volume was adjusted up to 100 ml with 0.1N HCl. Further 1ml of the above solution was diluted to 10 ml with 0.1N HCl and the absorbance of the resulting solution was observed at 275nm.

In vitro Buoyancy studies
The in vitro buoyancy was determined by floating lag time and total floating time (as per the method described by Rosa et al.) The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as the floating lag time (FLT) and the duration of time the tablet constantly floats on the dissolution medium was noted as the total floating time respectively (TFT).

Dissolution Study
The 900ml 0f 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temperature of 37°C $\pm$ 0.5°C. The tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 8hrs at 50 rpm. At definite time intervals, 5 ml of the dissolution fluid was withdrawn, filtered and again 5ml blank sample was replaced. Suitable dilutions were done with dissolution fluid and analyzed spectrophotometrically at 275 nm using a UV-spectrophotometer (Lab India).

Release Kinetics
The analysis of drug release mechanism from a pharmaceutical dosage from is an important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from FDDS was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

Zero Order Release Kinetics
It defines a linear relationship between the fraction of drug released versus time. $Q = k_o t$. Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics
Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process, suggested that the drug release from most of the slow release tablets could be described adequately by the first-

order kinetics. The equation that describes first order kinetics is ln (1-Q) = -K_1t.Where,Q is the fraction of the drug released at time t and K_1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug un dissolved against time will be linear if the release obeys the first order release kinetics.

Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time. $Q = K_2 t^{½}$ .Where, K_2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Flick's law, square root time dependant[19].

Power Law

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppa's and Korsemeyer equation (Power Law). $M_t/M_\alpha = K.t^n$.Where, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the M_t/M_α is the fraction of drug released at time t, K is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted in Table 2. A plot between log of M_t/M_α against log of time will be linear if the release obeys Papa's and Korsemeyer equation and the slope of this plot represents "n" value[20].

Similarity factor (f_2 analysis)

$f2 = 50. \log \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100\}$

Where 'R_t' and 'T_t' are the cumulative percentage drug dissolved at each of the selected n time point of the reference and test product respectively. The factor f2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The similarity factor f2 and its significance is shown in the Table 3a.

Fourier Transform Infrared Spectroscopy (FTIR) studies

The FTIR spectra of the drug (alone), and the drug-polymer(physical mixture) were recorded by the potassium bromide pellet method (Bruker model FTIR was used).The FTIR data of the pure drug is indicated in Table 3b.

RESULTS AND DISCUSSION

Evaluation of tablets

The objective of the present study was to prepare floating tablets of Atenolol. These tablets were developed to prolong the gastric residence time and to increase the drug bioavailability . Atenolol was chosen because it is better absorbed in the stomach than in the lower gastro intestinal tract. Totally, ten different formulations of Atenolol were prepared by using four different polymers like Guar gum, sodium alginate , HPMC 100cps,Carbopol 940, and diluents like lactose and dicalcium phosphate in different concentrations. The tablets were prepared by direct compression technique. The tablets were evaluated for physical characteristics: weight variation, hardness, friability, drug content, the floating lag time and the total floating time(Table 4). All the formulated tablets fulfilled the compendial specifications of weight variation, hardness, friability, drug content, floating lag time and the total floating time.

Dissolution study

The in vitro release characteristics of the tablets was evaluated for 8hrs. The amount of drug released from all the formulations depends on the concentration of the polymer used. Finally, the amount of drug released from all the formulations was found to be in the decreasing order(Fig.2-5),Sodium Alginate > HPMC100cps > Corbopol 940 > Guar gum Among all these formulations the F8 formulation(optimized formulation) containing sodium alginate and lactose showed the best result(drug content and in vitro dissolution studies).The result was compared with the branded formulation ,the result was satisfactory . The similarity factor (f2 value) calculated for the optimized formulation(F8) was found to be

70.74%,hence, its dissolution profile was similar to the dissolution profile of the branded extended release tablet.

Release Kinetics

The Table 5 enlists the coefficient of regression values of the different formulations. The values of n(diffusion exponent),K(release rate constant)and the dissolution parameters:T_{25}(time taken to release 25% of the drug),T_{50}(time taken to release 50% of the drug), T_{75} (time taken to release 75% of the drug), T_{90}(time taken to release 90% of the drug),computed for all the controlled release floating tablets and the marketed branded extended release tablet are represented in Table 6.To examine the release mechanism of Atenlol floating tablets, the results were analyzed according to the Korsemeyer – Peppa's equation. Release of Atenolol from the optimized formulation(F8) was found to follow first order kinetics (regression coefficient, r^2 = 0.982 to 0.988).Higuchi plot(for formulation ,F8, showed an "r^2" value of 0.996, suggesting that the diffusion and erosion plays an important role in the controlled release of the drug. The data was fitted to the Korsemeyer-Peppas equation; and the value of the diffusion exponent 'n' (0.26), for the formulation,F8, indicated that the drug release follows fickian diffusion.

FTIR studies

From the FTIR spectra it is clearly evident that there were no interactions of the drug and the polymer. The FTIR spectrum of the pure drug(Fig.6) shows the characteristic peaks at 3576.07 cm^{-1} and 584.33cm^{-1}. The FTIR spectrum of the drug and the polymer(sodium alginate),1:4 physical mixture(Fig.7) exhibited peaks at 3576.07cm^{-1} and 646.09cm^{-1}. This confirms the undisturbed structure of the drug in the formulation. This proves the fact that there is no potential incompatibility of the drug with the polymer used in the formulation. As the FTIR peaks of the pure drug were observed in the Drug: sodium alginate(polymer),1:4physical mixture, the drug-polymer interaction was absent.

CONCLUSION

The similarity factor calculated for the batch F8(optimized formulation) was 70.74%, and its dissolution profile was similar to the dissolution profile of the branded extended release tablet. The FTIR studies indicated the absence of the drug-polymer interaction in the optimized formulation. The best formulation F8 (was prepared using sodium. alginate and lactose) can successfully be employed as a controlled release floating drug delivery system. The floating tablets can control the fluctuations in the plasma drug concentration, increase the gastric residence time and eventually improve the bioavailability of the drug.

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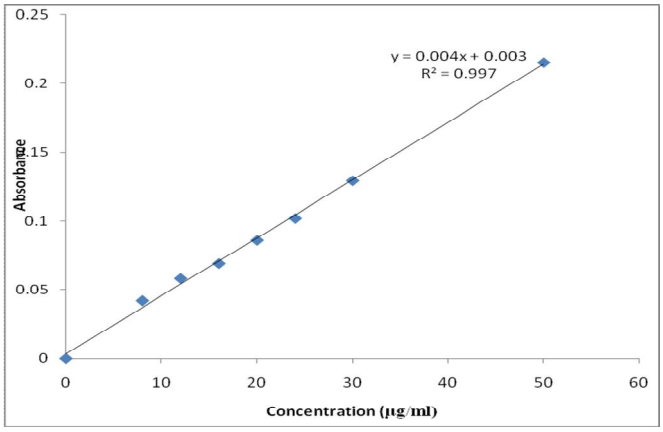

Fig. 1: Calibration curve of Atenolol in 0.1 N HCl (pH1.2)

Table 1: Composition of Different Formulations

FOR.CODE	Drug (mg)	Guargum (mg)	Sod. Alginate (mg)	HPMC 100cps (mg)	Corbopol-940 (mg)	Mag.stearate (mg)	Talc (mg)	$NaHCO_3$ (mg)	Lactose (mg)	DCP (mg)
F1	50	100	……	……	……	3	6	30	……	111
F2	50	100	……	……	……	3	3	60	……	134
F3	50	100	……	……	……	3	3	60	134	…….
F4	50	200	……	……	……	3.5	3.5	70	……	23
F5	50	200	……	……	……	3.5	3.5	35	……	58
F6	50	200	……	……	……	3.5	3.5	70	23	….
F7	50	……	200	……	……	3.5	3.5	70	……	23
F8	50	……	200	……	……	3.5	3.5	70	62	…….
F9	50	……	……	200	……	3.5	3.5	70	……	23
F10	50	……	……	……	200	3.5	3.5	70	……	23

Table 2: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion Exponent(n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-fickian) diffusion
0.89	Case II transport
n>0.89	Super Case II transport

Table 3a: Similarity factor f2 and its significance

S. No.	Similarity factor (f2)	Significance
1.	<50	Test and reference profiles are dissimilar.
2.	50 -100	Test and reference profiles are similar.
3.	100	Test and reference profiles are identical.
4.	>100	The equation yields a negative value.

TABLE 3b: Data for FTIR Spectrum of Atenolol

Functional Group	Frequency (cm^{-1})
OH	3353.35
O=C-NH_2	1646.77
H-N	3576.07
C=CH_2	886
C-H	2866.62
C-CH_3	2964.52

Table 4: Quality control parameters of Atenolol floating tablets

Formulation No:	Avg. Wt mean ± SD (n=20)	Hardness Kg/cm^2(n=3)	%Friability (n=20)	%Drug content (n=3)	Buoyancy lag time (min)	Total floating time (hrs)
F_1	298.4±0.4	4.76±0.20	0.110	90.1±2.5	.....	8
F_2	296.4±0.7	4.96±0.04	0.490	100±5.2	20	8
F_3	295.7±0.6	7.93±0.09	0.580	102±1.4	30	8
F_4	346.6±0.3	7.86±0.07	0.170	100±2.1	8	8
F_5	342.4±0.3	7.8±0.07	0.478	100.8±1.8	8	8
F_6	344.9±0.3	8	0.170	97.2±6.2	15	8
F_7	347.1±0.5	7.6±0.43	0.166	98.1±2.0	4	8
F_8	392.2±0.4	7.86±0.09	0.289	100.2±1.0	3	8
F_9	342.4±0.3	7.73±0.18	0.176	92.86±2.8	30	8
F_{10}	345.0±0.3	7.93±0.09	0.160	106.2±1.0	30	8

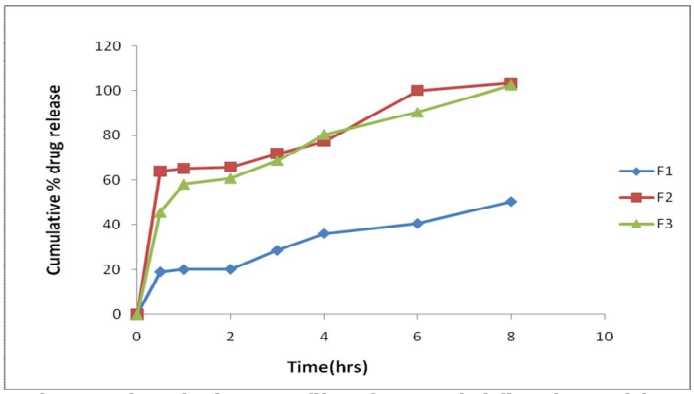

Fig. 2: Dissolution profile of Atenolol floating tablet (F_1, F2, F3) formulations

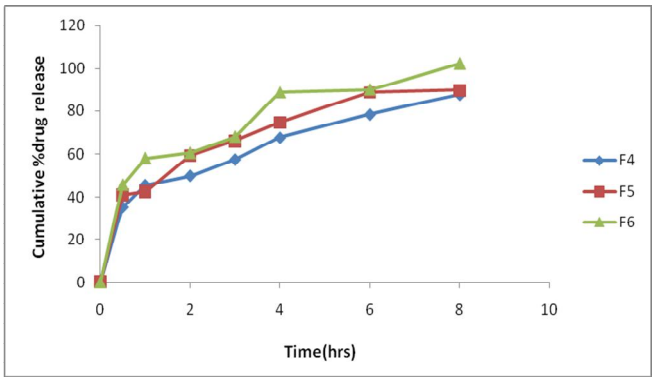

Fig. 3: Dissolution Profile of Atenolol Floating Tablets (F_4, F5, F6) Formulations

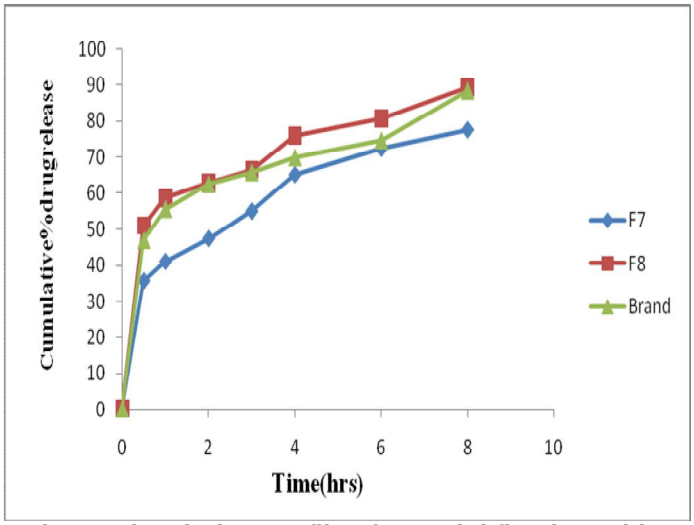

Fig. 4: Dissolution profile of atenolol floating tablet (F7, F8, Brand)Formulations

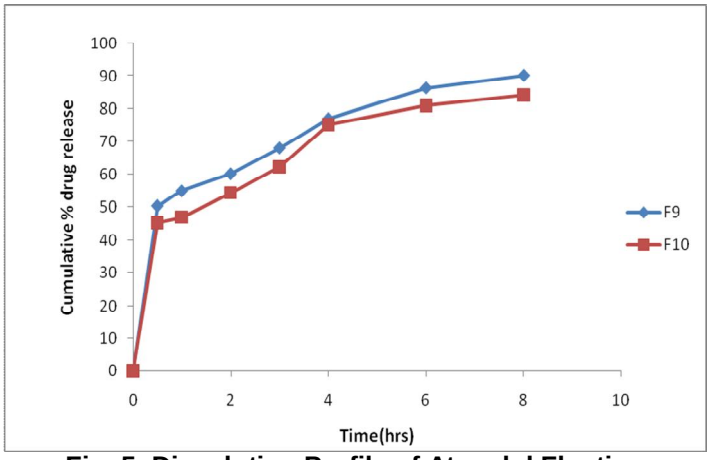

Fig. 5: Dissolution Profile of Atenolol Floating Tablets (F_9, F_{10}) Formulations

TABLE 5: Coefficient of regression (r^2) values of Atenolol floating tablets

Formulation	n	Dissolution Parameters					
		K_0(mg/hr)	K_1(hr^{-1})	T_{25}(hr)	T_{50}(hr)	T_{75}(hr)	T_{90}(hr)
F1	0.769	2.71	0.0.65	2.5	8	-----	-----
F2	0.192	6.0	0.200	0.2	0.4	3	-----
F3	0.400	8.0	0.232	0.25	0.65	3.5	6
F4	0.430	9.0	0.256	0.4	2.1	5.6	-----
F5	0.433	8.5	0.401	0.3	1.5	4	8
F6	0.361	2.5	0.556	0.25	2.3	3.3	6
F7	0.325	8.0	0.115	0.25	0.45	7	-----
F8	0.260	4.0	0.046	0.25	0.5	4	------
F9	0.352	8.8	0.118	0.25	1.6	3.75	-----
F10	0.366	7.28	0.165	0.25	0.6	4	-----
BRAND	0.230	3.32	0.111	0.25	0.6	6	------

Table 6: Dissolution Parameters of Atenolol Tablets

Formulation	Zero order	First order	Higuchi's	Peppa's
F1	0.983	0.984	0.924	0.978
F2	0.968	0.925	0.953	0.916
F3	0.985	0.975	0.958	0.985
F4	0.986	0.993	0.965	0.998
F5	0.959	0.982	0.985	0.984
F6	0.959	0.969	0.972	0.973
F7	0.975	0.992	0.993	0.987
F8	0.982	0.988	0.996	0.983
F9	0.979	0.994	0.991	0.973
F10	0.968	0.981	0.978	0.965
BRAND	0.974	0.962	0.985	0.986

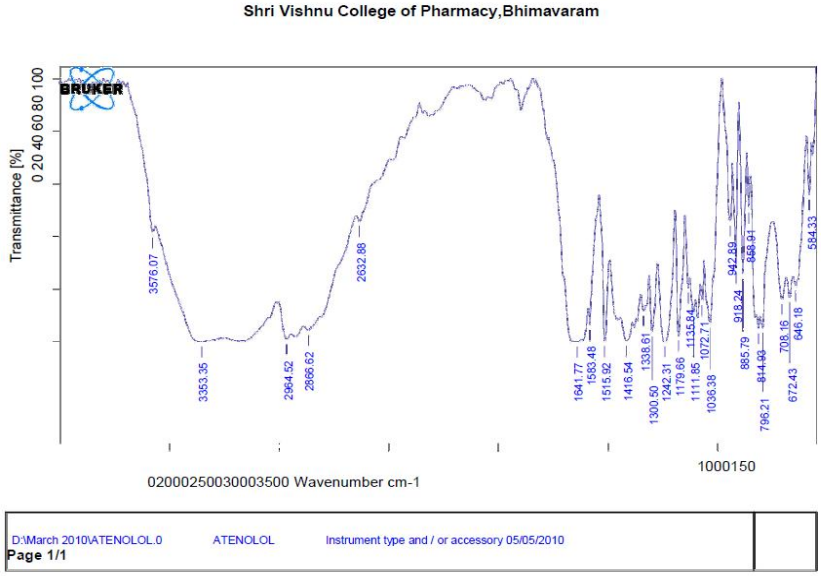

Fig.6: FTIR spectrum of Atenolol

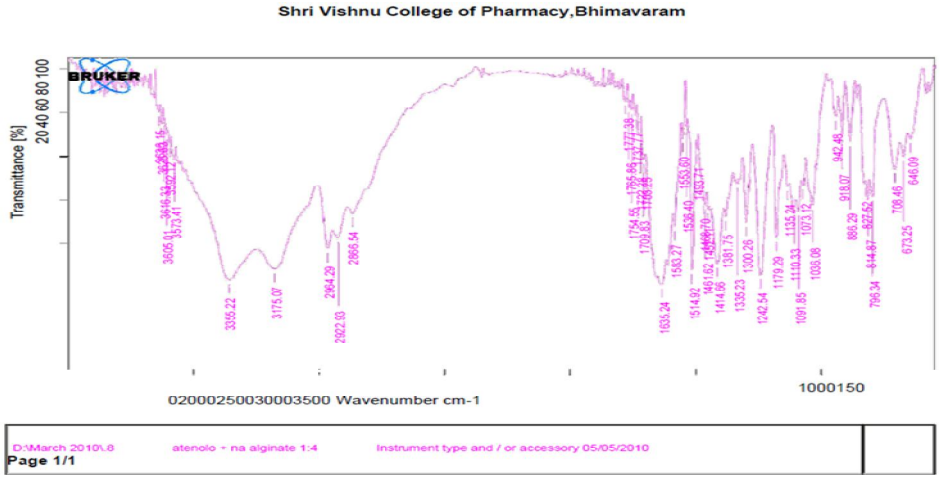

Fig.7: FTIR spectrum of atenolol and sodium alginate physical mixture

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