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PREPARATION AND CHARACTERIZATION OF POLYMERIC MATRIX DIFFUSIONAL RECTAL PATCHES OF ATENOLOL

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ABSTRACT

Antihypertensive suffer from the disadvantages of extensive first pass metabolism and variable bioavailability, so they were considered ideal Patch candidate. Atenolol, a β-adrenergic receptor antagonist, has been shown to be safe and effective in the treatment of patients with hypertension. It has a mean plasma half-life of 6 hrs and only 45% of the orally administered drug reaches the circulation due to hepatic metabolism. A model reported predicts that mean plasma Atenolol concentration of 43, 99 and 175 ng/ml are required to produce a 20%, 30%, and 40% reduction in blood pressure respectively. The aim of present investigation is to formulate and optimize the Atenolol matrix diffusion controlled rectal drug delivery system. In the present investigation, the influence of various grades and concentration of polymers were studied. Study was carried out to formulate an elegant product exhibiting desired therapeutic performance, from a small and cute dosage form. In order to achieve this goal, following criteria were set; the dosage form should remain intact for a period of 24hr. Drug is delivered in a controlled manner. The size of dosage form should be small with a view to enhance convenience of patient as well as compliance to therapy. Plasma concentration should achieve within short period of time.

KEYWORDS

Anti-hypertensive, Atenolol, Matrix Diffusion Controlled and Therapeutic Response.

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INTRODUCTION

Atenolol can be estimated by various methods such as UV Spectroscopy, HPLC, HPTLC etc. In the present investigation Atenolol was estimated by UV Spectrophotometry.

Determination of Lambda-Max

A solution of Atenolol was prepared in 0.01N HCl and UV spectrum was taken using Shimadzu UV/VIS double beam spectrophotometer. UV spectrum of was recorded by scanning 5 µg/ml solution of Atenolol in 0.01N Hydrochloric acid and scanned between 200-400 nm.

Preparation of Calibration Curve

The calibration curve of Atenolol in 0.01N HCl was prepared by measuring the absorbance of the solution in the range of 20-100 µg/ml. the absorbance of the solution was measured at 273.5 nm.

Atenolol (100mg) was dissolved in 40ml 0.01N HCl and volume was made up to 100ml using 0.01N HCl in 50 ml volumetric flask. This stock solution (1mg/ml) was further diluted with 0.01N HCl to obtained solution of 20 to 100 µg/ml. Absorbance of each solution was measured at 273.5 nm using Shimadzu UV/VIS Spectrophotometer with 0.01N HCl as a reference standard. The standard curve was generated for entire range of 20 to 100 µg/ml. The experiment was performed in triplicate and based on average absorbance; the equation for the best line fit was generated.

Determination of Lambda-Max

The UV maxima of resultant solution were measured with Shimadzu UV- 2201 UV/VIS Spectrophotometer. Figure No.1 shows the UV spectrograph of Atenolol in 0.01N HCl.

Calibration Curve

The calibration curve of Atenolol in 0.01N HCl was prepared by measuring the absorbance of the solution in the range of 20-100 µg/ml. the absorbance of the solution measured at the wavelength 273.5 nm. The results of standard curve are shown in Table No.1 and Figure No.2.

Preformulation Studies

The physiochemical properties of Atenolol were determined using following parameters.

Determination of Melting Point

Melting point of drug was determined using capillary tube closed at one end and placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed in triplicates and average value was noted.

Solubility Studies

The solubility studies were performed in phosphate buffer solution, pH 7.4, in distilled water, methanol, chloroform, ether, alcohol (95%), acetone, acetic acid, Isopropanol, Dioxane, acetonitrile and ethyl acetate separately by adding excess amounts of drug in each case and keeping the excess drug containing flasks on a water bath shaker NSW-133 for 24hr at 32^{o}C.

Infrared (IR) Spectroscopic Analysis

In the preparation of film formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Atenolol and the selected polymers. The individual drug and drug with excipients were scanned separately.

The Fourier Infrared (FTIR) spectrums of moisture free samples were recorded on IR spectrophotometer by potassium bromide (KBr) pellet method. The scanning range was 4000 to 400 cm^{-1} and the resolution was 1 cm^{-1}. Potassium bromide was mixed with drug and polymer and the spectra were taken. FT-IR spectrum of Atenolol was compared with FR-IR spectra of Atenolol with polymers. Disappearance of Atenolol peaks or shifting of peak in any of the spectra was studied.

Differential Scanning Calorimetry Analysis

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced during transformation of state (i.e., endothermic or exothermic phase transformation). DSC curves for pure drug Atenolol, Eudragit RL100 and Eudragit RS100 mixture and their composites were recorded using DSC-Shimadzu 60 with TDA trend line software. Drug and polymer was weighed (7-10 mg) and heated at a scanning rate of 10^{o}C min under dry nitrogen flow (100 ml/min) between 50-350^{o}C. Aluminum pans and lids were used for drug sample. Pure water and indium were used to calibrate the DSC temperature scale and enthalpy response.

Melting Point

Melting point of Atenolol was found to be 154 ± 2.5^{o}C (average of three readings). This value is same as that of the literature citation**.**

Solubility Study

Solubility of Atenolol was evaluated in different solvent. The results are mentioned in Table No.2.

Infrared (IR) Spectroscopic Analysis

FT-IR spectroscopic studied was carried out to assess any interaction between the drug and the excipients. The chemical interaction between the drug and the polymer often leads to identifiable changes in the Infrared (IR) profile of complexes. The FT- IR spectrum of pure Atenolol is shown in Figure No.3. The FT-IR spectra of atenolol with Ethylene vinyl acetate copolymer (Vinyl acetate 40%), Ethyl cellulose, Eudragit RL100, Eudragit RS.100 are shown in Figure No.4, the presence or absence of characteristics peaks associated with specific structural groups of the drug molecule as noted. From the FTIR spectra it was revealed that no interaction occurred between Atenolol and different polymers.

Differential scanning calorimetric analysis

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced during transformation of state (i.e., endothermic or exothermic phase transformation). DSC curves for pure drug Atenolol was shown in figure 5(a). DSC curve of ERS 100, ERL 100 and Atenolol composite are shown in Figure 5(c). Pure powdered Atenolol showed a melting endotherm at 158.95^{o}C temperature. DSC scan of ERL100 and ERS100 showed a broad endotherm due to the presence of residual moisture in polymers. DSC thermogram of Atenolol with ERL100 and ERS100 exhibits endothermic peaks at near to 161.80^{o}C temperature. Results reveal absence of any interaction occurring between drug and polymers.

MATERIALS AND METHODS

Preparation of Polymeric Matrix Rectal Device of Atenolol

Matrix-type Rectal patches containing Atenolol were prepared using different polymers (Table No.4).The polymers were weighed in requisites ratios keeping the total polymer weight 800 mg, and dissolved in a given solvent. Di-n-butyl Phalate (30% w/w of polymer composition) were used as a plasticizer. Atenolol (533.33mg) was added and mixed using a mechanical stirrer. The uniform dispersion of polymeric solution of drug (10 ml) was poured on the mercury pool. Solvent was evaporated at room temperature, and matrices were carefully lifted. Laminates were punched out to have a 3.14 cm^2 area. Laminates were affixed on polyethylene coated aluminum foil backing. The release face of medicated laminate was covered with peelable silicone liner. The devices were stored in desiccators, at room temperature until further used[3].

Physiochemical Evaluation of Polymeric Matrix Device

Prepared Atenolol containing matrices were evaluated for various parameters like thickness, weight variation, drug content, flatness, folding endurance, moisture content, moisture absorption, % WVTR etc.

RESULTS AND DISCUSSION

The present investigation deals with the development of Atenolol loaded polymeric matrix using different polymers. The preliminary screening was carried out for the selection of best polymer. A diffusion mediated matrix controlled rectal drug delivery system for Atenolol was successfully prepared using different polymers using mercury substrate method and all matrices were evaluated using different physiochemical parameters.

Thickness

With the help of micrometer (0.001mm), Mitutoyo, Japan, the thickness of film was measured at six different points and the average thickness was noted. The results of thickness measurements are given in Table No.5. The results indicate that there was no much difference in the thickness with in the formulations. Thickness in the different formulations was in the range of 182.5 ± 2.5 μm to 85.0 ± 2.5 μm. Maximum thickness was found in formulation F1, while minimum found in formulation F4. These results revealed that thickness was found to increase as hydrophobic portion of polymer increases. The results of thickness measurements also indicate uniform distribution of the drug and polymer over

the mercury surface. The rank order of thickness of Atenolol loaded polymeric matrices was EVA (40% VA) copolymer > ERS 100 > ERL100:ERS100 (1:1)> EC: PVP (2:3) >ERL 100: HPMC (2:3).

Weight Variation

Drug loaded films (3.14cm2) were weighed using Sartorius electronic balance (Model P-224 S), Shimadzu, Japan and the results of weight variation are given in Table No.6. The weight of 3.14 cm2 film ranged from 50.30 ± 0.100 mg to 58 ± 0.500 mg. The weight of the patches was found to be uniform among different batches.

In a weight variation test, the pharmacopoeial limit for the percentage deviation of all the films of less than mg is ± 10%. The average percentage deviation of all formulations was found to be within the limit, and hence all the formulation passed the test for weight variation as per official requirements. All the formulations showed acceptable pharmaco-technincal properties. From the results obtained, it was clear that there was proper distribution of Atenolol in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulation, with small deviation.

Flatness

The flatness was measured manually for the prepared films. An ideal patch should be formulated in such a way that it possesses a smooth surface and it should not constrict with time. Flatness studies were performed to assess the same. The results of the flatness study showed that none of the formulations had the differences in the strip length before and after their cuts. It indicates 100% flatness observed in the formulated patches. Thus, no amount of constriction was observed in the film of any formulation and it indicates smooth flat surface of the patches and thus they could maintain a smooth surface when applied on to the skin.

Folding Endurance

Folding endurance was determined manually for drug loaded polymeric matrices. The folding endurance of the films was determined by repeatedly folding a strip measuring 2x2 cm size at same place till it break. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. The results of folding endurance are given in Table No.7. Here formulation F1, F2 and F3 shows good folding endurance as compare to formulation F4 and F5.

Moisture Content (Loss on Drying)

The moisture content was determined by keeping the drug loaded polymeric matrices patches in desicator containing activated silica for 24h. The percentage moisture content was calculated from the weight differences relative to the final weight. The results of the moisture content studies for different formulations are shown in Figure No.7.

The moisture content in all the formulations was found to be low and ranged from 0.571 ± 0.013 to 4.103 ± 0.210 %. The result revealed that the moisture content was found to increase with increasing concentration of hydrophilic polymers. The small moisture content in the formulations helps them to maintain texture.

The rank order of % moisture content of Atenolol loaded polymeric matrices were EVA (VA 40%) copolymer < ERS 100 < ERL100:ERS100 (1:1) < EC: PVP (2:3)>ERL 100: HPMC (2:3).

Moisture Absorption

% Moisture absorption was determined by keeping the drug matrices in a desiccators containing 200 ml saturated solution of Sodium chloride (Relative humidity of 75%) at normal room temperature for 72hr. The final weight was noted when there was no further change in the weight of individual patch. The percentage moisture absorption as calculated as a difference between final and initial weight with respect to initial weight. The results of the moisture content studies for different formulations are shown in Figure No.8.

The moisture absorption in all the formulations was found to be low and ranged from 0.7400 ± 0.0360 to 5.8734 ± 0.1706. The results revealed that the moisture absorption was found to increase with increasing concentration of hydrophilic polymers. The rank order of % moisture absorption for Atenolol loaded matrices were EVA (VA 40%) copolymer < ERS 100 < ERL100:ERS100 (1:1) < EC: PVP (2:3) <ERL100: HPMC (2:3).

Water Vapor Transmission Rate (%WVTR)

The water vapor transmission rates of different formulation were evaluated, the results are shown in Figure No.9. Atenolol films containing ERL100: HPMC showed higher % WVTR as compared to other polymers. This may be due to the hydrophilic nature of ERL 100 and HPMC. Formulation F1 and F2 showed less % WVTR as compared to F4 and F5. The rank order of % water vapor transmission rate for Atenolol loaded polymeric matrices were EVA (VA 40%) copolymer < ERS 100 < ERL100:ERS100 (1:1) < EC: PVP (2:3) <ERL100: HPMC (2:3).

***In Vitro* Diffusion Study of Atenolol Loaded Matrix Diffusional Films**

The release rate determination is one of the most important studies to be conducted for all controlled release delivery systems. The diffusion study of patches is very crucial, because one needs to maintain the drug concentration on the surface of stratum corneum consistently and substantially greater than the drug concentration in the body to achieve a constant rate of drug permeation.

Experimental

An *in vitro* diffusion study of Atenolol from various polymeric matrices was studied using modified Keshary-Chien diffusion cell[4]. The effective permeation area of the diffusion cell and receptor cell volume was 3.14cm^2 and 40 ml, respectively. The temperature was maintained at 37 ±0.5^{o}C. The receptor compartment contained 40 ml of 0.01N HCl stirred by magnetic stirrer.

Samples (2 ml) were withdrawn and replaced with the same volume of fresh receptor solution, through the sampling port of the diffusion cell at different time intervals. The absorbance of the withdrawn samples were measured using UV VIS spectrophotometer at 237.5 nm using 0.01N HCl as a blank. The experiments were done in triplicate. Amount of drug released per square centimeter of patch were plotted against function of square root of time for different formulations. The release rate Q/√T was determined by simple regression analysis of steady state data.

RESULTS AND DISCUSSION

Diffusion studies are important for ensuring the sustained release performance and the reproducibility of rate and duration of drug release. *In vitro* release profile is an important tool that predicts in advance, the extent of concentration builds up in vivo. The results of *in vitro* drug diffusion studies from Rectal patches are depicted in Table No.8 and Figure No.10.

The results of diffusion study of Atenolol released from polymeric matrix, formulated using various polymers are presented in Table No.8 and profiles are shown in Figure No.10. The release rate Q/√T **(**μg/cm^2 √hr) was determined by simple regression analysis of steady state data. The release of Atenolol from all the matrices followed square root law. The rank order of release were EVA (VA 40%) copolymer < ERS 100 < ERL100:ERS100 (1:1) < EC: PVP (2:3) < ERL100: HPMC (2:3).

The in vitro permeation experiment indicated that when the hydrophilic polymer concentration increased, the amount of drug permeation increased. Initial rapid dissolution of the hydrophilic polymers occurs when the patch is in contact with the hydrated skin, resulting in the accumulation of high amount of drug on the skin surface and thus leading to the saturation of the skin with drug molecule at all the time.

Formulation F1 EVA (VA 40%) copolymer exhibited minimum Q/√T release rate (434.45 μg/cm^2√h) while Formulation F5 exhibited maximum Q/√T release rate (1337.80 μg/cm^2√h). The physiochemical property of polymer plays important role in drug release characteristics, from the polymeric matrix. EVA (VA 40%) copolymer is more hydrophobic as compare to other polymers and exhibited reduced permeation from the matrix. It was observed that as the concentration of hydrophilic polymer increased in the formulation the rate of diffusion increased subsequently. “Burst effect” was observed in the formulation F4 and F5 and this may be due to sufficient solubility of drug in the polymer.

***In Vitro* Release Kinetics**

The release data was fitted into various mathematical models using software to know which mathematical model will best fit to obtained release profiles. The obtained R values for various models are given in Table No.9. The process of drug release in most controlled release devices including rectal patches is governed by diffusion and the polymer matrix has a strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymers chain. The *in vitro* release profile could be best expressed by Higuchi's equation for the permeation of drug from the matrix.

Table No.1: Calibration curve of Atenolol in 0.01N HCl at 273.5nm

S.No	Concentration (µg/ml)	Absorbance
1	0	0.000 (0.000)
2	20	0.101 (0.005)
3	40	0.184 (0.002)
4	60	0.275 (0.001)
5	80	0.365 (0.006)
6	100	0.445 (0.007)
Correlation coefficient = 0.9992		
Absorbance = 0.0044 x concentration + 0.0063		
Values in parenthesis indicates standard deviation (n=3)		

Table No.2 Solubility of Atenolol in different solvents

S.No	Solvent	Solubility
1	Methanol	Soluble
2	Acetic acid	Soluble
3	Dimethyl sulfoxide	Soluble
4	Methanol: Acetone (3:7)	Soluble
5	Ethanol (96%)	Sparingly soluble
6	Water	Slightly soluble
7	Isopropanol	Slightly soluble
8	Acetone	Very Slightly soluble
9	Dioxane	Very Slightly soluble
10	Acetonitrile	Insoluble
11	Ethyl acetate	Insoluble
12	Chloroform	Insoluble

Table No.3: FT-IR Spectral data of Atenolol [2]

S.No	Frequency (cm-1)	Assignment
1	3346.61	-CO-NH-
2	3153.72	-CO-NH-
3	2964.69	C-H stretching (alkane)
4	1643.41	C=O stretching (amide)
5	1516.10	-N-C=O, amide
6	1417.73	H2N-CO-
7	1377.22	C-O stretching (alcohols)
8	1244.13	Arylether
9	1178.55	i-pr

Table No.4: Composition of prepared films

S.No	Formulation code	Polymers	Plasticizers (30% w/w of polymer composition)	Solvent
1	F1	EVA (VA 40%) copolymer	----------	2ml acetic acid and 10 ml toluene
2	F2	ERS100	DBP	Methanol
3	F3	ERL100: ERS100(1:1)	DBP	Methanol
4	F4	EC:PVP (2:3)	DBP	Methanol
5	F5	ERL 100:HPMC (2:3)	DBP	Methanol

Table No.5: Results of thickness uniformity of F1 to F5 film formulations

S.No	Formulation Code	Average thickness (µm)			
		Trial 1	Trial 2	Trial 3	Mean ± S.D.*
1	F1	180.0	185.0	182.5	182.50 ± 2.500
2	F2	165.0	165.0	162.5	164.16 ± 1.443
3	F3	122.5	125.0	120.0	122.50 ± 2.500
4	F4	115.0	112.5	115.0	112.50± 1.443
5	F5	85.0	87.5	82.5	85.00 ± 2.500

***Standard deviation, n=3**

Table No.6: Results of weight variations of F1 to F5 film formulations

S.No	Formulation Code	Average weight (mg)			
		Trial 1	Trial 2	Trial 3	Mean ± S.D.*
1	F1	52.4	52.5	52.1	52.33 ± 0.208
2	F2	55.3	55.8	55.6	55.56 ± 0.251
3	F3	58.3	58.7	58.5	58.50 ± 0.200
4	F4	50.6	50.1	50.9	50.53 ± 0.404
5	F5	53.5	53.1	53.7	53.43 ± 0.305

***Standard deviation, n=3**

Table No.7: Results of folding endurance of F1 to F5 film formulations

S.No	Formulation Code	Folding endurance			
		Trial 1	Trial 2	Trial 3	Mean ± S.D.*
1	F1	248	250	247	248.33 ± 1.527
2	F2	108	110	112	110.00 ± 2.000
3	F3	55	50	57	54.00 ± 1.000
4	F4	19	17	18	18.00 ± 1.000
5	F5	35	38	45	39.33 ± 5.131

***Standard deviation, n=3**

Table No.8: *In vitro* diffusion profiles of Atenolol from different polymer matrix

S.No	Time ($hr^{½}$)	Cumulative amount of drug release from device (µg/cm2)				
		Formulation code				
		F1	F2	F3	F4	F5
1	0.707	473.34 ± 25.67	726.48 ± 29.40	1060.46 ± 35.78	1120.23 ± 39.56	1210.39 ± 42.56
2	1	571.56 ± 25.46	990.49 ± 35.78	1370.89 ± 55.39	1459.23 ± 55.29	1678.34 ± 60.43
3	1.414	731.22 ± 31.56	1320.40 ± 51.34	1870.45 ± 60.99	1953.34 ± 61.64	2169.90 ± 71.34
4	1.732	890.56 ± 35.67	1570.30 ± 55.78	2241.36 ± 71.64	2321.90 ± 71.56	2541.20 ± 80.43
5	2	1025.89± 40.79	1810.37 ± 59.88	2564.90 ± 79.45	2659.86 ± 79.40	2958.68 ± 100.50
6	2.236	1136.30± 64.99	1950.34 ± 64.99	2863.94 ± 90.57	3045.75 ± 80.38	3245.46 ± 106.34
7	2.449	1200.13 ± 51.34	2160.80 ± 70.01	3090.34 ± 101.45	3320.00 ± 48.67	3458.95 ± 78.46
8	Q/√T (µg/cm2 √hr)	434.45	810.72	1220.90	1265.00	1337.80
9	R	0.9958	0.9989	0.9917	0.9963	0.9936

Table No.9: Data of various parameters of model fitting of formulations

S.No	Formulation	Zero order equation	First order equation	Higuchi's equation
1	F1	0.9804	0.9470	0.9962
2	F2	0.9836	0.9440	0.9985
3	F3	0.9836	0.9404	0.9998
4	F4	0.9935	0.9606	0.9968
5	F5	0.9835	0.9503	0.9977

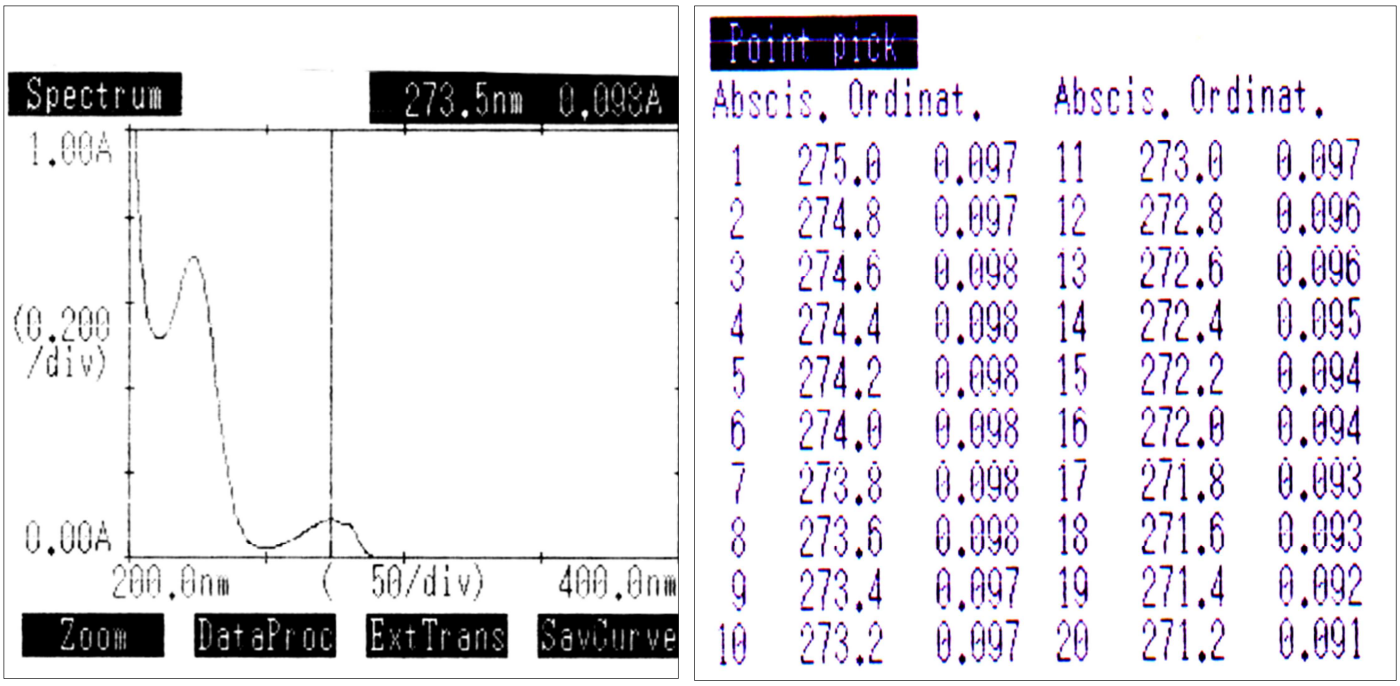


Figure No.1: UV spectrograph of Atenolol in 0.01N HCl

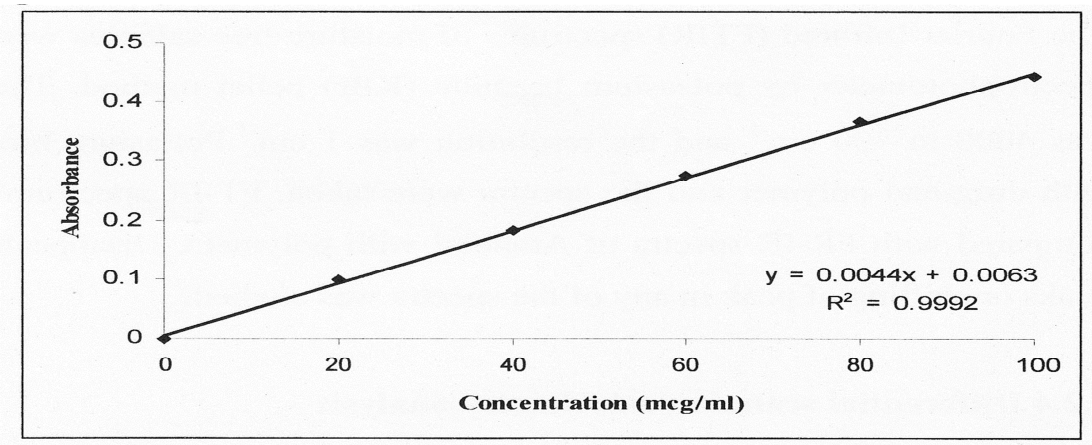


Figure No.2: Calibration curve of Atenolol in 0.01N HCl at 273.5nm

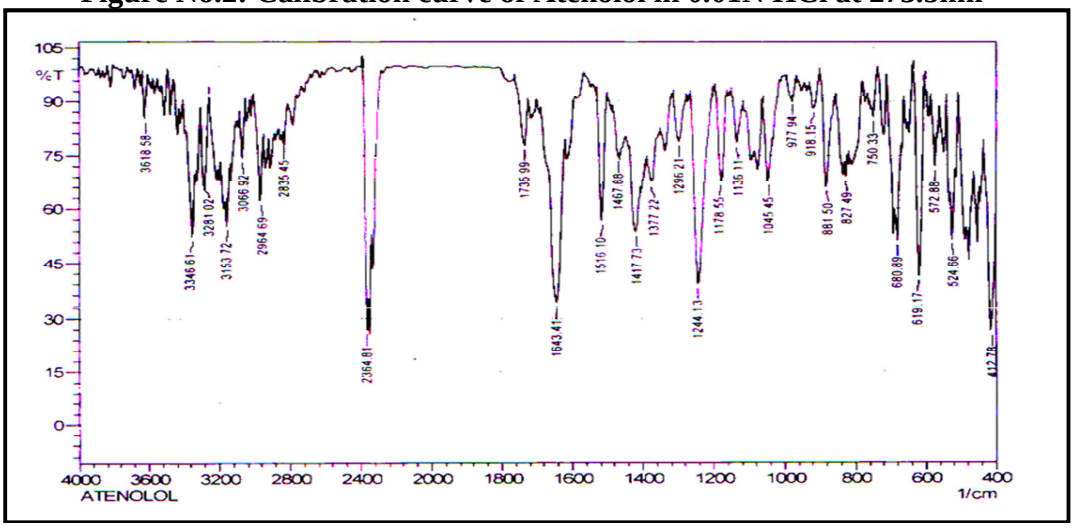
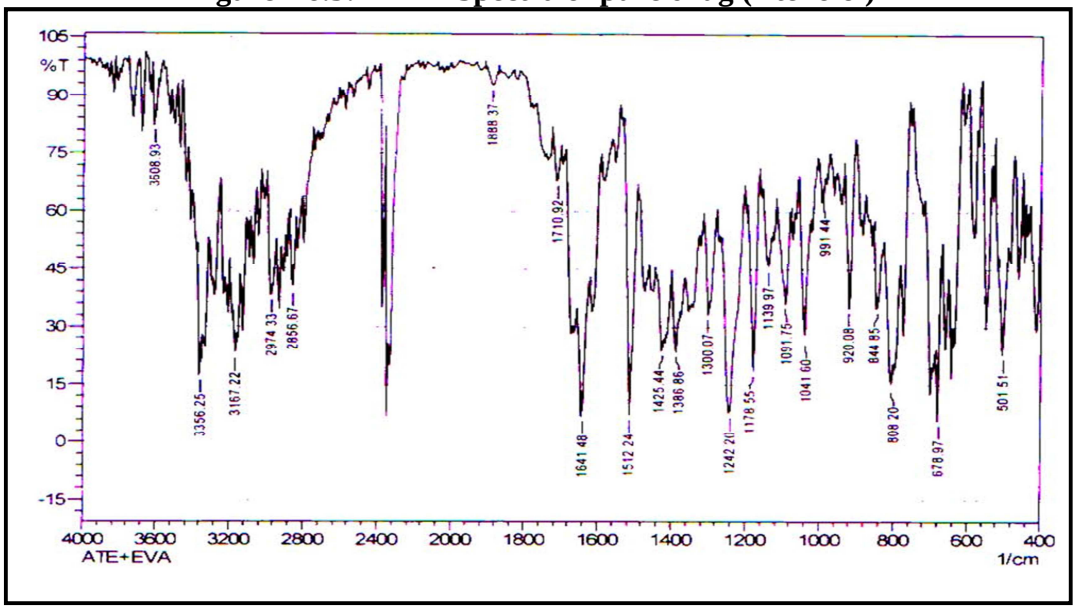


Figure No.3: FT-IR Spectra of pure drug (Atenolol)



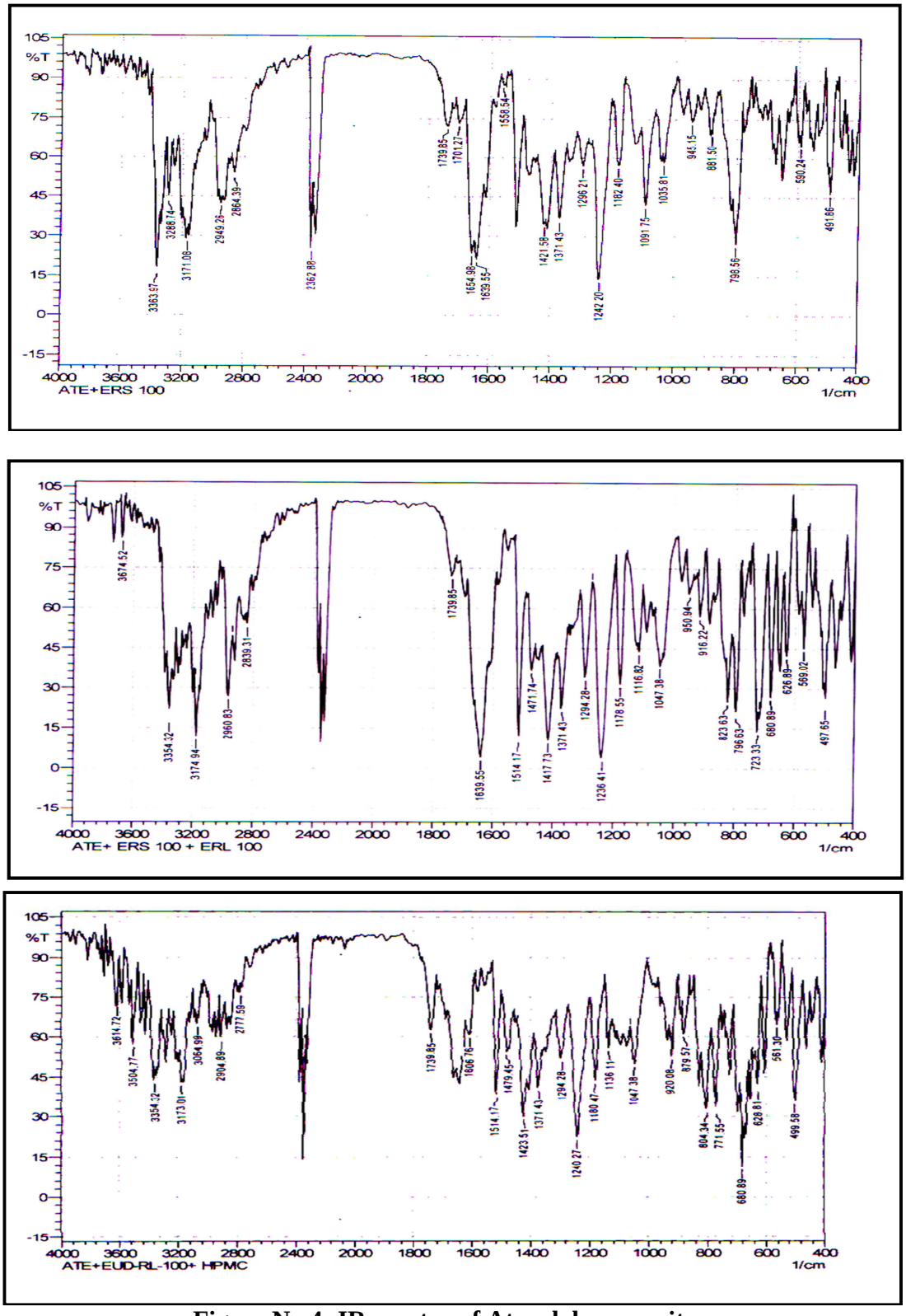


Figure No.4: IR spectra of Atenolol composites

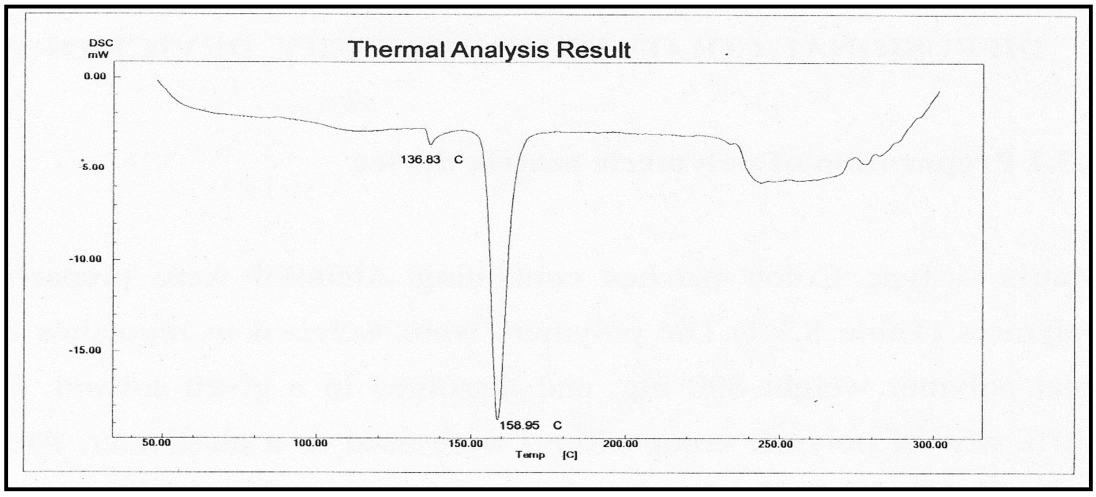


Figure No.5 (a): DSC thermogram of Atenolol

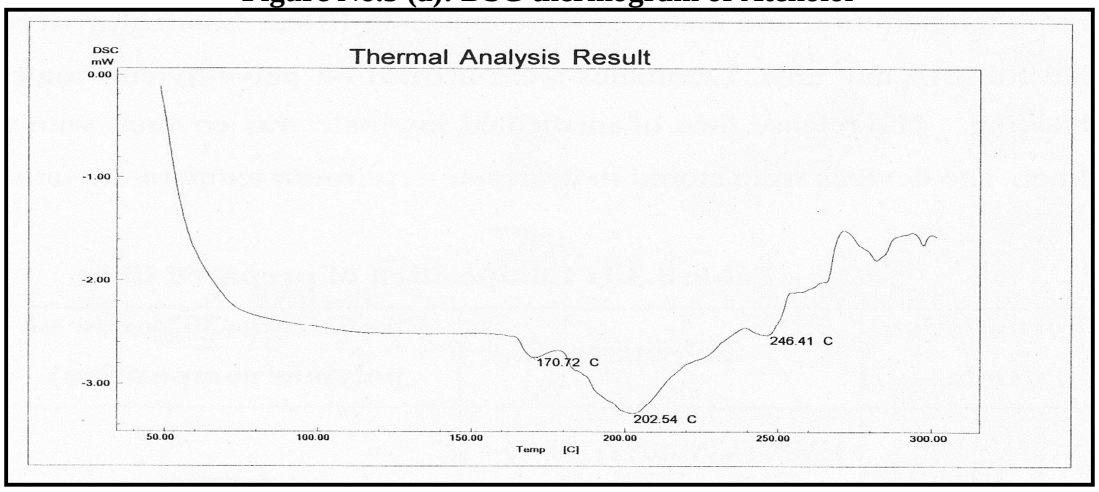


Figure No.5 (b): DSC thermogram of ERL100 and ERS 100

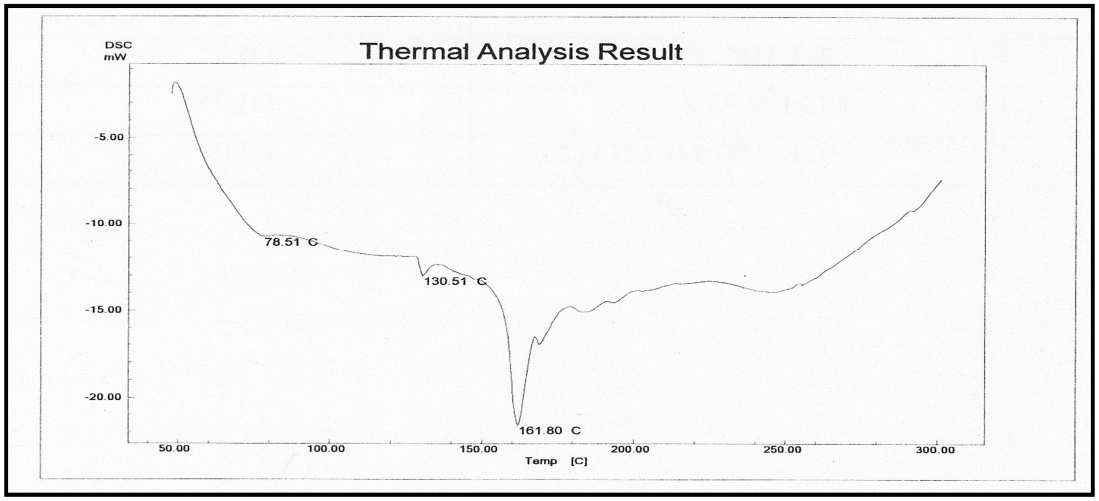


Figure No.5(c): DSC thermogram of Atenolol composite

Figure No.6: Matrix diffusional rectal patch of Atenolol

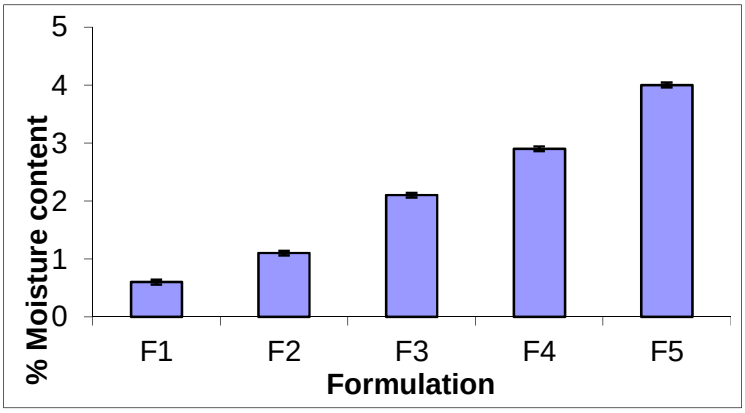


Figure No.7: % moisture content in drug loaded polymeric matrices of Atenolol

CONCLUSION

The importance of polymer dissolution on drug release from matrices has been known for ensuring the controlled release performance and the reproducibility of rate and duration of drug release. Initial "burst release" was observed in patches F4 and F5. This may be because of the much higher % of hydrophilic polymer. This hydrophilic components allow faster release of drug exhibiting small "time lag" to establish a concentration profile in the patches resulting in a "burst effect" in diffusion studies[6,7]. When burst release as well as higher release rate was considered, formulation F4 and F5 may be avoided from the preparation of a physiochemically stable and controlled release patch type formulation. Formulation F1 and F2 gave the slowest release. Thus it can be reasonably be suggested that the formulation **F3** is best suited for further in vitro permeability study through human live skin[8,9].

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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