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Development and in vitro evaluation of sustained release formulation of telmisartan hydrochloride

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Abstract

The aim of the present study was to develop sustained release formulation of Telmisartan HCl to maintain constant therapeutic levels of the drug for over 12 hrs. Eudragit RL 100, Guar gum and ethyl cellulose were employed as polymers. Telmisartan HCl dose was fixed as 20 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 30, 60 and 90 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 96.10 % in 12 hours. Optimized formulation drug release was fitted into different drug release kinetics, it followed zero order release kinetics mechanism.

Keywords: Telmisartan HCL, Eudragit RL 100, Guar gum, Ethyl cellulose, Sustained release tablets.

INTRODUCTION

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. Modified release delivery systems may be divided conveniently in to four categories.

Delayed release

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-

coated tablets where timed release is achieved by a barrier coating.

Sustained release

During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

Controlled release

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

Extended release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds

Site specific targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

Receptor targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

Design and formulation of oral sustained release drug delivery system

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion. Sustained (zero-order) drug release has been attempted to be achieved with various classes of sustained drug delivery system

AIM AND OBJECTIVE

Aim of the study is to formulate and evaluate Telmisartan HCl sustained release tablets using different polymers such as Guar gum, Ethyl cellulose and various grades of polymethacrylate polymers. Microcrystalline cellulose as diluents

METHODOLOGY

Analytical method development

Determination of absorption maxima

100mg of Telmisartan HCl pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml) and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation of calibration curve

100mg of Telmisartan HCl pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20 and 25 µg/ml of Telmisartan per ml of solution. The absorbance of the above dilutions was measured at 232 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2)which determined by least-square linear regression analysis.

Table 1: Formulation chart Fourier transform infrared (FTIR) spectroscopy

Form No.	Telmisartan	β cyclodextrin	Eudragit RL 100	Guar gum	Ethyl cellulose	Mag. Stearate	Talc	MCC pH 102
F1	20	15	30	-	-	3	3	244
F2	20	15	60	-	-	3	3	86
F3	20	15	90	-	-	3	3	116
F4	20	15	-	30	-	3	3	56
F5	20	15	-	60	-	3	3	86
F6	20	15	-	90	-	3	3	116
F7	20	15	-	-	30	3	3	56
F8	20	15	-	-	60	3	3	86
F9	20	15	-	-	90	3	3	96

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

The quality of tablet, once formulated by rule, is s to prolong the release of Telmisartan. Total weight of the tablet was considered as 300mg.

Evaluation of post compression parameters for prepared tablets

- Weight variation test
- Thickness
- Hardness
- Friability

Formulation composition for tablets

Determination of drug content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Formulation development of tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 1.The tablets were prepared as per the procedure given below and aim i UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Dissolution parameters

Apparatus -- USP-II, Paddle type

Dissolution Medium -- 0.1 N HCl pH 1.2, p H 6.8 Phophate buffer

RPM -- 50

Sampling intervals (hrs)

0.5,1,2,3,4,5,6,7,8,10,11,12

Temperature -- 37°c $\pm$ 0.5°

Procedure

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$

0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 232 and 233nm using UV-spectrophotometer.

Application of release rate kinetics to dissolution data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$F = K_o t$ Where, 'F' is the drug release at time 't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics

The release rate data are fitted to the following equation Log (100-F) = kt A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

F = k t1/2 Where, 'k' is the Higuchi constant. In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$M_t/ M_\infty = K t^n$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0;while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport),n=1; and for super case II transport, n > 1.In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-crowell release model

$(100-Q_t)^{1/3}= 100^{1/3}– K_{HC}.t$ Where, k is the Hixson-Crowell rate constant. Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULTS AND DISCUSSION

The present study was aimed to developing Sustained release tablets of Telmisartan using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical method

Graphs of Telmisartan were taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 232 nm and 233 nm respectively.

Table 2: Observations for standard graph of telmisartan in 0.1N Hcl (232nm)

Conc [µg/ml]	Absorbance
0	0
5	0.104
10	0.205
15	0.302
20	0.411
25	0.503

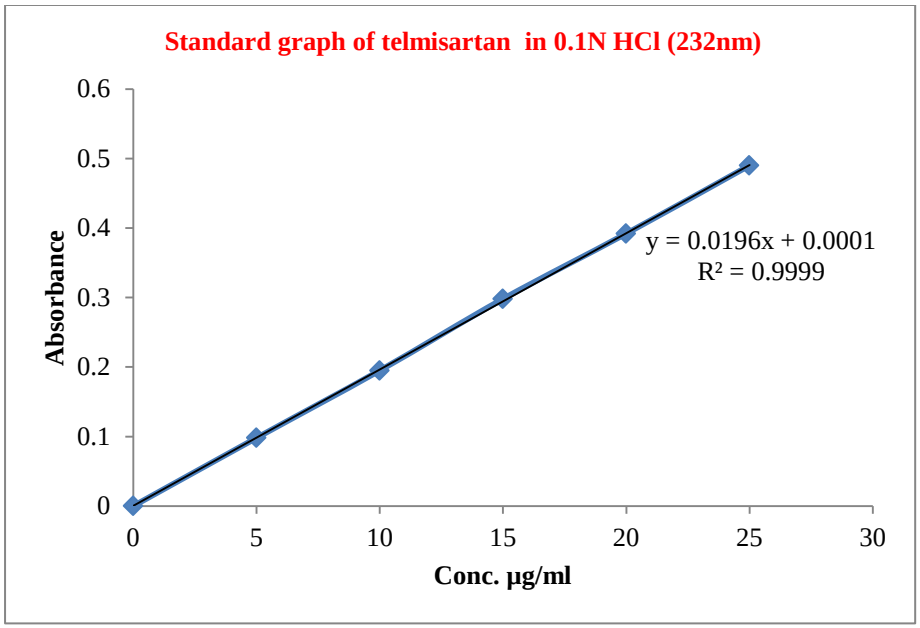

Fig 1: Standard graph of Telmisartan in 0.1N HCl

Table 3: Observations for graph of Telmisartan in pH 6.8 phosphate buffer (233nm)

Conc [µg/l]	Abs
0	0
5	0.098
10	0.195
15	0.298
20	0.392
25	0.490

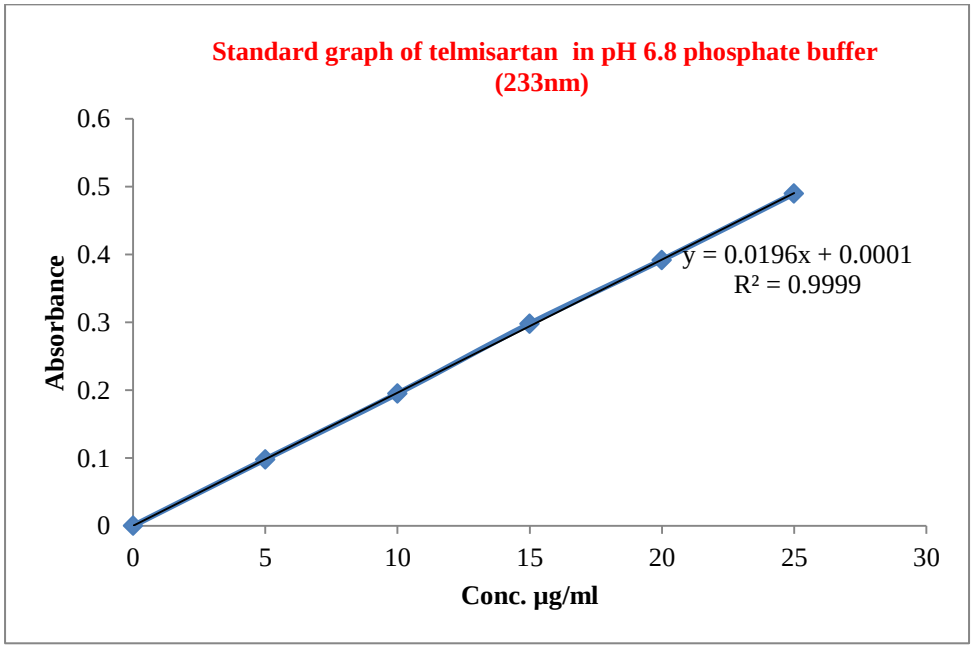

Fig 2: Standard graph of Telmisartan pH 6.8 phosphate buffer (233nm

Drug – Excipient compatability studies Fourier transform-infrared spectroscopy

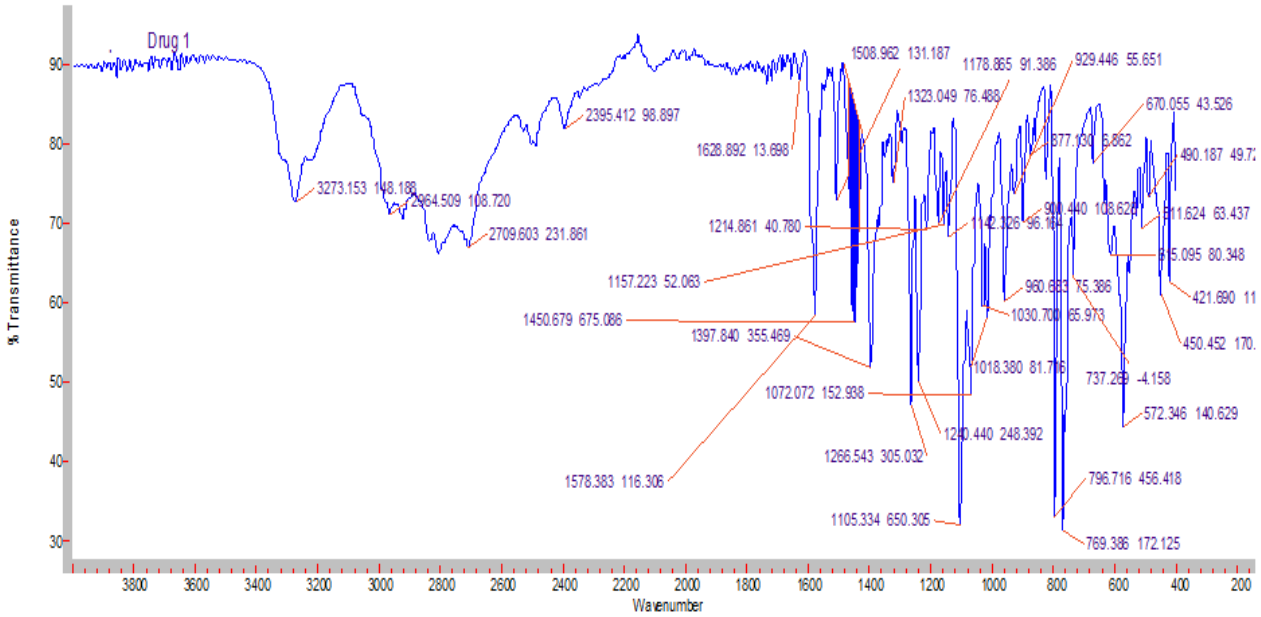

Fig 3: FT-TR Spectrum of Telmisartan pure drug

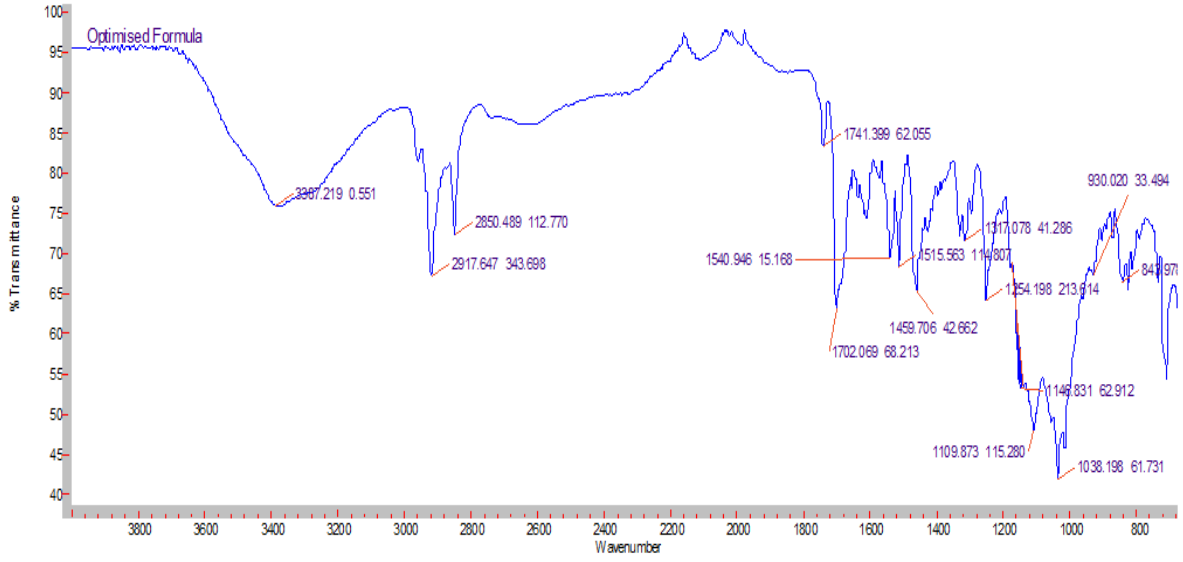

Fig 4: FT-IR Spectrum of Optimised Formulation

Table 4: Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.04	0.54±0.04	16.21±0.06	1.10±0.06
F2	25.67	0.42±0.09	0.52±0.04	16.87±0.05	1.23±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	1.16±0.03
F4	25.43	0.51±0.06	0.59±0.07	17.67±0.08	1.15±0.04
F5	25.34	0.47±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.49±0.06	0.59±0.04	16.43±0.05	1.2±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.45±0.08	0.52±0.03	17.54±0.09	1.15±0.02

Pre-formulation parameters of core blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.42±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.52±0.04 to 0.67±0.02 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality control tests

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table 5: Quality control tests

Formulation	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	312.5	4.5	0.50	3.8	99.76
F2	305.4	4.5	0.51	3.9	99.45
F3	308.6	4.4	0.51	3.9	98.34
F4	300.6	4.5	0.55	3.9	98.87
F5	309.4	4.4	0.56	3.7	99.14
F6	310.7	4.5	0.45	3.7	98.56
F7	302.3	4.1	0.51	3.4	98.42
F8	301.2	4.3	0.49	3.7	99.65
F9	298.3	4.5	0.55	3.6	99.12

***In-vitro* quality control parameters for tablets**

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 6: *In-vitro* drug release studies

Time (hr)	Cumulative percent drug dissolved								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	25.5	20.1	16.4	17.25	16.42	14.62	10.4	9.4	8.5
1	46.7	33.4	23.7	38.26	25.73	19.86	16.5	15.6	14.5
2	76.5	45.3	31.6	54.16	36.63	22.35	28.6	21.4	18.4
3	98.4	56.3	40.4	72.01	45.04	31.45	39.5	36.7	23.4
4		77.3	53.4	88.26	58.25	39.80	48.5	42.4	28.2
5		89.4	59.4	97.10	65.33	45.25	59.4	49.6	34.8
6		95.34	65.4		76.41	58.24	69.2	55.3	40.2
7			71.5		84.84	66.73	74.5	60.3	44.8
8			87.3		97.80	71.34	82.3	72.8	50.4
9			97.45			75.52	87.78	83.52	63.34
10						82.17	98.78	88.65	69.27
11						87.10		96.56	74.86
12						96.10			79.97

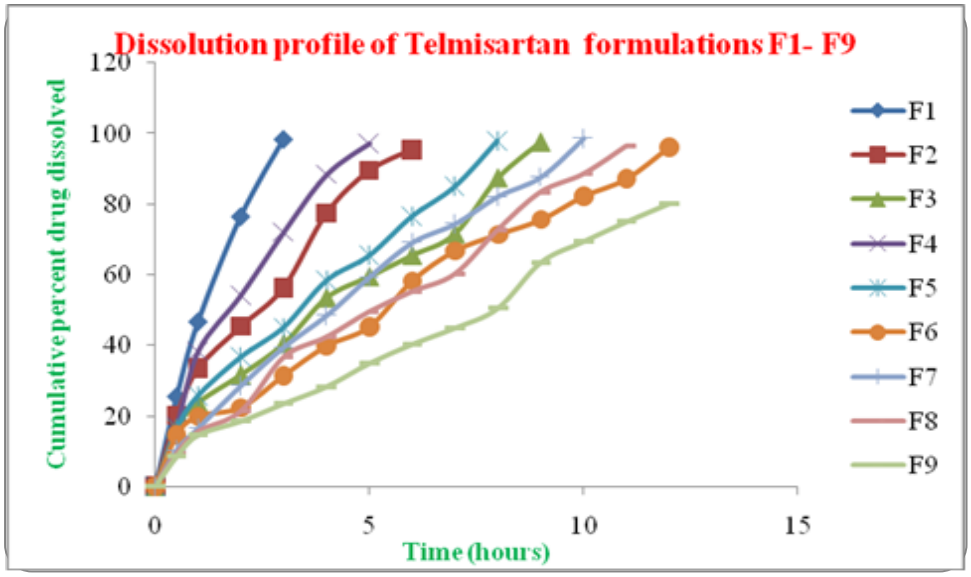

Fig 5: *In-vitro* drug release studies

Application of release rate kinetics to dissolution data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 7: Release rate kinetics

Cumulative (%) release q	time (t)	Log (%) release	log (%) remain	release rate (cumulative % release / t)	1/cum% release	peppas log q/100	% drug remaining
0	0		2.000				100
14.62	0.5	1.165	1.931	29.240	0.0684	-0.835	85.38
19.86	1	1.298	1.904	19.860	0.0504	-0.702	80.14
22.35	2	1.349	1.890	11.175	0.0447	-0.651	77.65
31.45	3	1.498	1.836	10.483	0.0318	-0.502	68.55
39.8	4	1.600	1.780	9.950	0.0251	-0.400	60.2
45.25	5	1.656	1.738	9.050	0.0221	-0.344	54.75
58.24	6	1.765	1.621	9.707	0.0172	-0.235	41.76
66.73	7	1.824	1.522	9.533	0.0150	-0.176	33.27
71.34	8	1.853	1.457	8.918	0.0140	-0.147	28.66
75.52	9	1.878	1.389	8.391	0.0132	-0.122	24.48
82.17	10	1.915	1.251	8.217	0.0122	-0.085	17.83
87.1	11	1.940	1.111	7.918	0.0115	-0.060	12.9
96.1	12	1.983	0.591	8.008	0.0104	-0.017	3.9

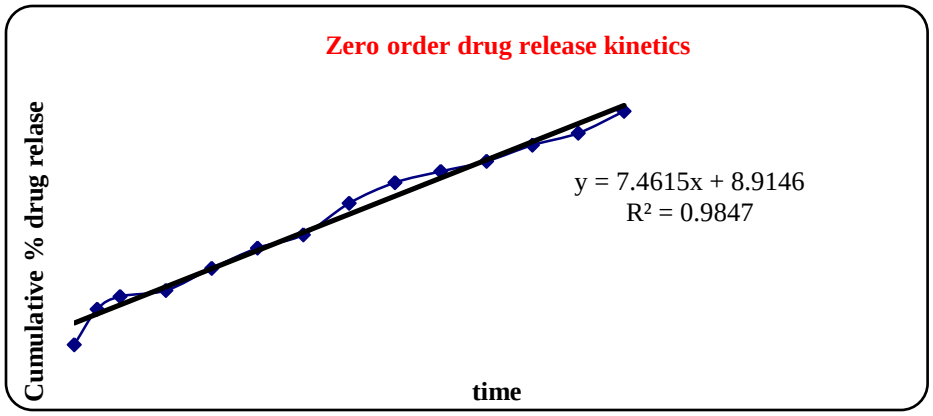

Fig 6: Zero order release kinetics graph for F6

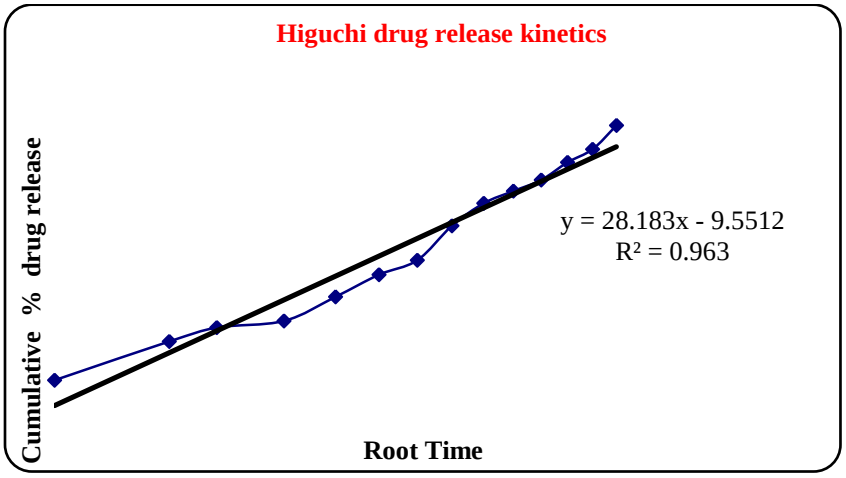

Fig 7: Higuchi release kinetics graph for F6

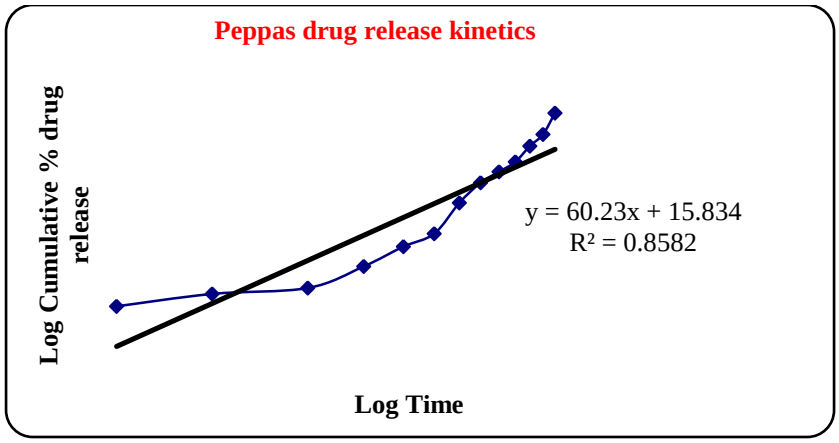

Fig 8: Peppas release kinetics graph for F6

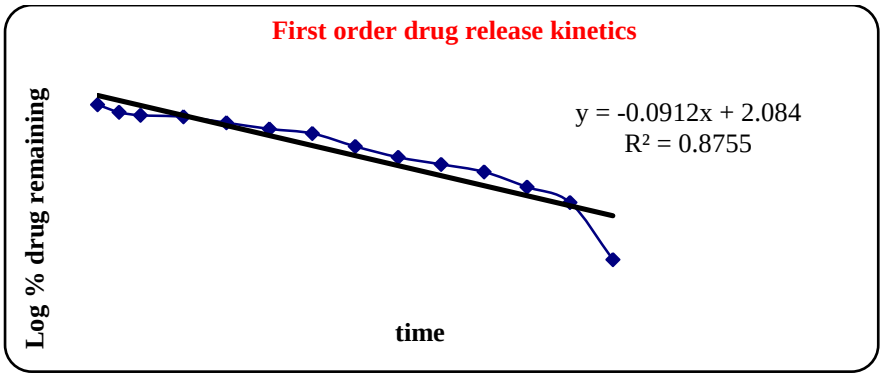

Fig 9: First order release kinetics graph for F6

From the above graphs it was evident that the formulation F6 was followed Zero order release kinetics.

CONCLUSION

The aim of the present study was to develop sustained release formulation of Telmisartan HCl. Eudragit RL 100, Guar gum and ethyl cellulose were employed as polymers. Telmisartan HCl dose was fixed as 20 mg. Total weight of the tablet was 300 mg. Polymers were used in the concentration of 10, 20 and 30 % concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 96.10 % in 12 hours. The drug release pattern followed zero order release kinetics mechanism.

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