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Formulation of Isoniazide Sustained Release Formulation by Using Carbopol 934 P

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ABSTRACT:

The aim of the present study was to develop sustained release formulation of Isoniazide to maintain constant therapeutic levels of the drug for over 12 hrs. Various polymers such as Guar gum, HPMCK100 M, PEG 6000 and Carbopol 934 p were employed as polymers. Isoniazide dose was fixed as 100 mg. Total weight of the tablet was considered as 400 mg. Polymers were used in the concentration of 100, 150 and 200 mg. All the formulations 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. It followed zero order release kinetics.

1. Introduction

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug (Venkateshwara et al., 2015).

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action Figure 1 (Niraj et al., 2015). An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus, after absorption allows maintenance of plasma concentration within a therapeutic range, which minimizes side effects and also reduces the frequency of administration of drug (Tania Munjal et al., 2012).

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits (Rathore, A.S. et al., 2013, Rajak et al., 2011).

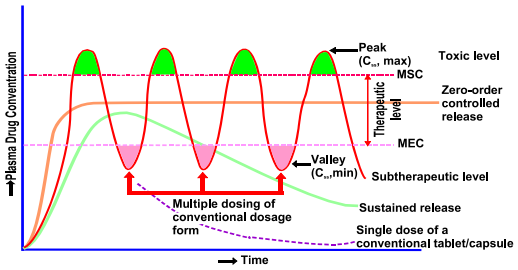

Figure 1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration) (Anka Rao et al., 2015).

Isoniazide also known as isonicotinylhydrazine (INH), is an organic compound that is the first-line medication in prevention and treatment of tuberculosis.

Once activated, isoniazide inhibits the synthesis of mycoloic acids, an essential component of the bacterial cell wall. At therapeutic levels isoniazide is bactericidal against actively growing intracellular and extracellular Mycobacterium tuberculosis organisms. Specifically isoniazide inhibits InhA, the enoyl reductase from Mycobacterium tuberculosis, by forming a covalent adduct with the Nicotinamide adenine dinucleotide(NAD) cofactor. It is the INH-NAD adducts that acts as a slow, tight-binding competitive inhibitor of InhA (Sridhar Babu et al., 2014).

2. Materials and methods

Isoniazide was obtained as gift sample from hetero labs hyderabad and Guargum ,Carbopol, HPMC MCC pH 102, Magnesium stearate and Talc were procured from merck.

2.1. Analytical method development:

2.1.1 Determination of absorption maxima:

A solution containing the concentration 10 µg/ml drug was prepared in 0.1N HCl 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.

2.1.2 Preparation calibration curve:

100mg of Isoniazide pure drug was dissolved in 100ml of 0.1 N HCl (stock solution)10ml of solution was taken and make up to 100ml with 0.1 N HCl (100µg/ml). From this 10ml was taken and make up to 100 ml with 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 5,10,15,20,25,30,35 and 40µg/ml of Isoniazide per ml of solution. The absorbance of the above dilutions was measured at 256 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 is determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions (Amol R. Jipkate et al., 2011).

2.2 Drug – excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples were 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 (Chella Naveen et al., 2012).

2.3 Preformulation parameters

The quality of tablet, once formulated by rule, is 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 were tested as per Pharmacopoeia (D. Pavani et al., 2015).

2.3.1 Angle of repose:

The angle of repose was calculated using the following formula:

$\tan \theta = h / r$

$\tan \theta$ = Angle of repose, h = Height of the cone, r = Radius of the cone base

2.3.2 Bulk density:

The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where, M = weight of sample, V_o = apparent volume of powder

2.3.3 Tapped density:

The tapped density was calculated, in gm per L, using the formula:

$Tap = M / V$

Where, Tap= Tapped Density, M = Weight of sample, V= Tapped volume of powder

2.3.4 Measures of powder compressibility:

Compressibility Index is calculated using the following formulas:

Carr's Index = $[(tap - b) / tap] \times 100$

Where, b = Bulk Density, Tap = Tapped Density

2.4 Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 6.3. The tablets were prepared as per the procedure given below and aim is to prolong the release of Isoniazide. Total weight of the tablet was considered as 400 mg.

Table 1: Formulation composition for tablets

Formulation No.	Isoniazide	Guar Gum	HPMC K100M	PEG 6000	Carbpol 934	Mag. Stearate	Talc	MCC pH 102
F1	100	100				4	4	QS
F2	100	150				4	4	QS
F3	100	200				4	4	QS
F4	100		100			4	4	QS
F5	100		150			4	4	QS
F6	100		200			4	4	QS
F7	100			100		4	4	QS
F8	100			150		4	4	QS
F9	100			200		4	4	QS
F10	100				100	4	4	QS
F11	100				150	4	4	QS
F12	100				200	4	4	QS

All the quantities were in mg

2.4 Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content (Rama Rao et al., 2016, Shanmugan et al., 2015, Bandameedi et al., 2015).

2.5.1 Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

2.5.2 Hardness:

For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

2.5.3 Thickness:

Average thickness for core and coated tablets is calculated and presented with deviation.

2.3.4 Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability. It is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

2.3.5 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 isoniazide 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 water. The solution was suitably diluted and the absorption was determined by UV–Visible spectrophotometer. The drug concentration was calculated from the calibration curve (Ashwini Rajendra et al., 2012).

2.3.6 *In vitro* drug release studies

Dissolution parameters:

Apparatus -- USP-II, Paddle Method

Dissolution Medium -- 0.1 N HCl, 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 ± 0.5°c

As the preparation was for sustained drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

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 ± 0.5°c. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 2 hours and then the medium 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 of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 256 nm using UV-spectrophotometer (Hareesh et al., 2015).

2.5 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 (Suvakanta Dash et al., 2010)

2.4.1 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.

2.4.2 First order release rate kinetics:

The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

2.4.3 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.

2.4.4 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 supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

2.4.5 Hixson-Crowell release model:

$$(100\text{-}Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$$

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) (B. Ramu et al., 2015).

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3. Results and Discussion

The present study was aimed to develop sustained release tablets of Isoniazide using various polymers. All the formulations were evaluated for physicochemical properties and in-vitro drug release studies.

3.1. Analytical method

Graphs of Isoniazide was taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 256 nm and 260 nm respectively.

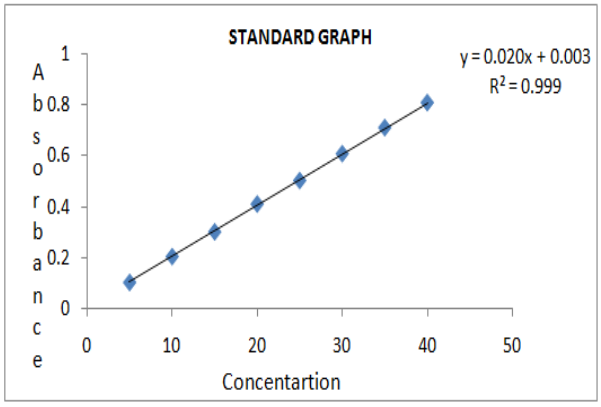

Figure 2: Standard graph of Isoniazide in 0.1N HCl

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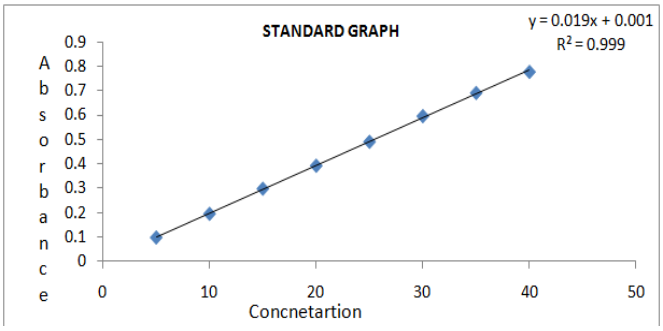

Figure 3: Standard graph of Isoniazide pH 6.8 phosphate buffer (260nm)

3.2. Drug – Excipient compatability studies

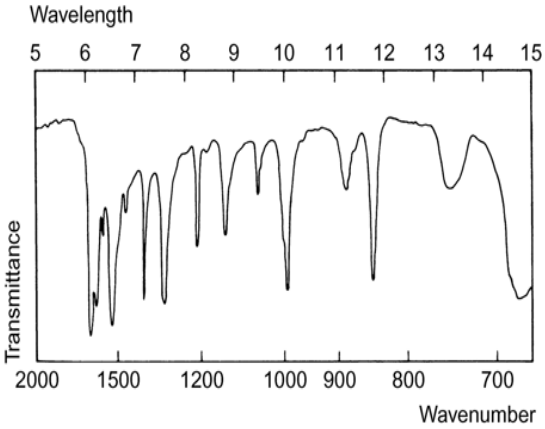

Figure 4: FT-IR Spectrum of Isoniazide pure drug

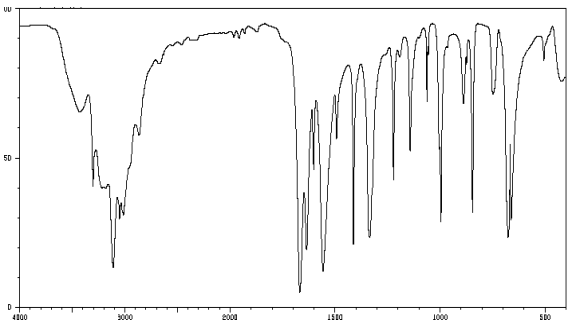

Figure 5: FT-IR Spectrum of Optimised Formulation

3.3. Preformulation parameters of powder 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 0.43±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 0.57 to 0.69 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 (Table 2).

3.4. Quality Control Parameters For tablets:

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 3).

3.5. *In-Vitro* Drug Release Studies

From the dissolution data it was evident that the formulations prepared with Sodium CMC as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with HPMCK100M retarded the drug release in the concentration of 200 mg (F6) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation. The formulations prepared with PEG 6000 showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered (Table 4).

3.6. 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 (Table7).

Table 2. 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	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±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	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02
F10	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F11	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F12	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09

Table 3.Invitro quality control parameters for tablets

Formulation codes	**Weight variation(mg)**	**Hardness(kg/cm2)**	**Friability (%loss)**	**Thickness (mm)**	**Drug content (%)**
F1	412.5	4.5	0.50	6.8	99.76
F2	405.4	4.5	0.51	6.9	99.45
F3	398.6	4.4	0.51	4.9	99.34
F4	410.6	4.5	0.55	6.9	99.87
F5	409.4	4.4	0.56	6.7	99.14
F6	410.7	4.5	0.45	6.5	98.56
F7	402.3	4.1	0.51	6.4	98.42
F8	401.2	4.3	0.49	6.7	99.65
F9	398.3	4.5	0.55	6.6	99.12
F10	410.6	4.5	0.55	6.9	99.87
F11	409.4	4.4	0.56	6.7	99.14
F12	410.7	4.5	0.45	6.5	98.56

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

Table 4: Dissolution Data of Isoniazide Tablets Prepared With Guar gum In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F1	**F2**	**F3**
0.5	25.5	20.1	16.4
1	46.7	39.4	26.7
2	76.5	55.3	34.6
3	98.4	75.3	42.4
4		87.3	55.4
5		99.4	67.4
6			85.4
7			91.5
8			97.3

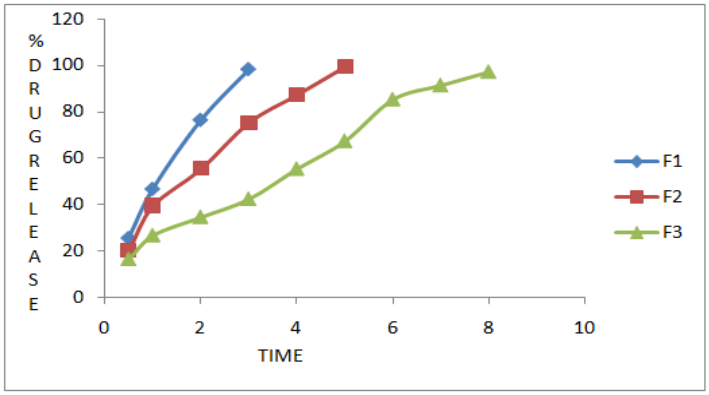

Figure 6: **Dissolution profile of Isoniazide (F1, F2, F3 formulations).**

Table 5: **Dissolution Data of Isoniazide Tablets Prepared With HPMCK100 M In Different Concentrations**

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F4	**F5**	**F6**
0.5	17.25	16.42	14.62
1	38.26	25.73	19.86
2	54.16	36.63	22.35
3	72.01	45.04	31.45
4	88.26	58.25	39.80
5	97.10	65.33	45.25
6		76.41	58.24
7		84.84	66.73
8		97.80	71.34
9			75.52
10			82.17
11			87.10
12			96.10

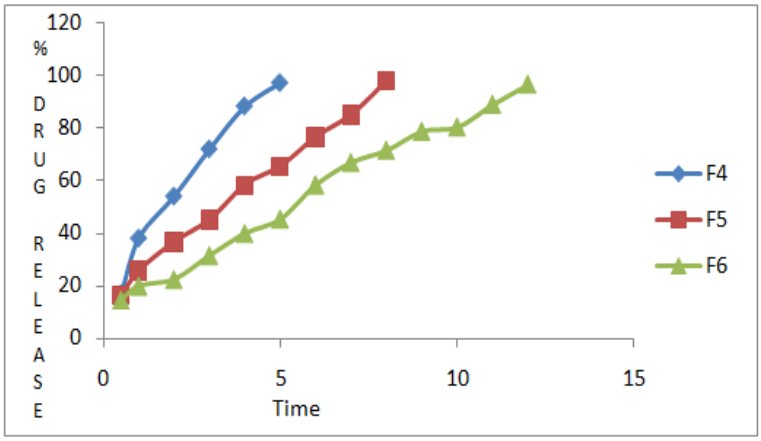

Figure 7: **Dissolution profile of Isoniazide (F4, F5, F6 formulations)**

Table 6: Dissolution Data of Isoniazide Tablets Prepared With PEG6000 In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3+SD)		
	F7	**F8**	**F9**
0.5	10.4	9.4	8.5
1	16.5	15.6	14.5
2	28.6	21.4	18.4
3	39.5	36.7	23.4
4	48.5	42.4	28.2
5	59.4	49.6	34.8
6	69.2	55.3	40.2
7	74.5	60.3	44.8
8	82.3	72.8	50.4
9	87.78	83.52	63.34
10	98.78	88.65	69.27
11		96.56	74.86
12			79.97

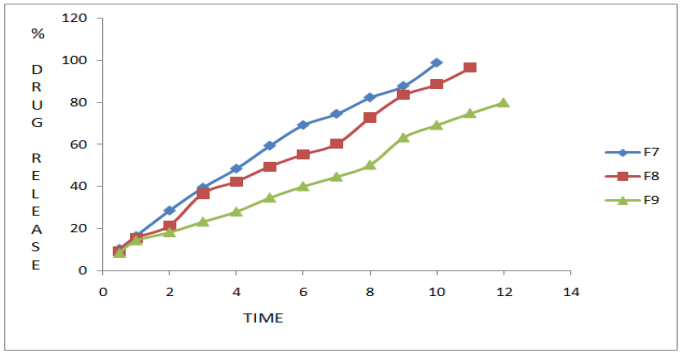

Figure 8: Dissolution profile of Isoniazide (F7, F8, F9 formulations)

Table 7: Release kinetics data for optimised formulation

UMULATIVE (%) 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	1.256	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

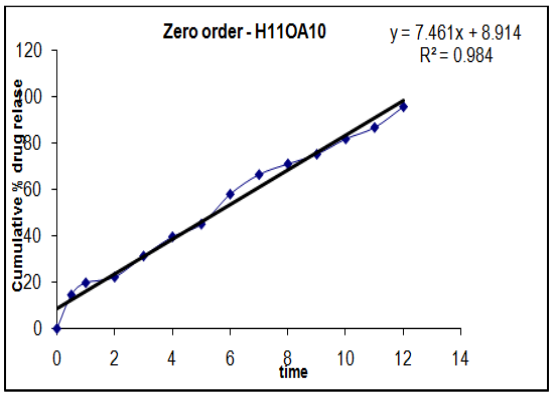

Figure 9 : Zero order release kinetics graph

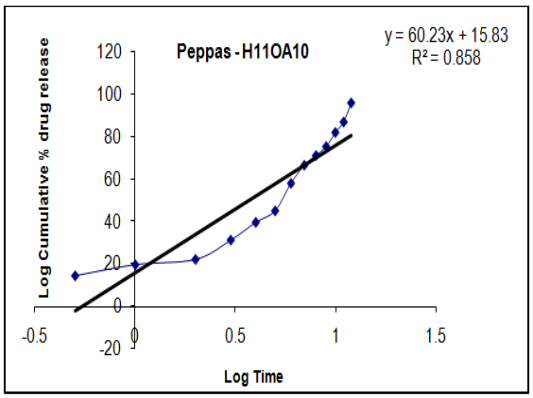

Figure 11: Kars mayer peppas graph

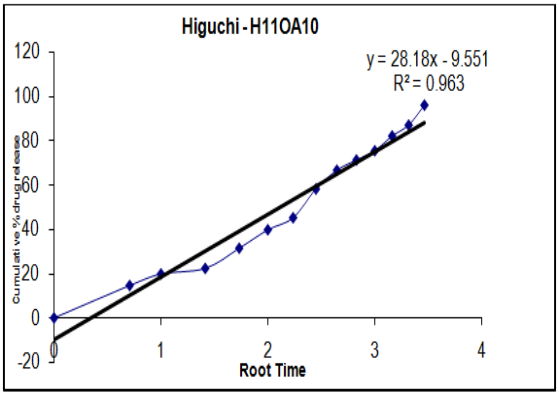

Figure 10 : Higuchi release kinetics graph

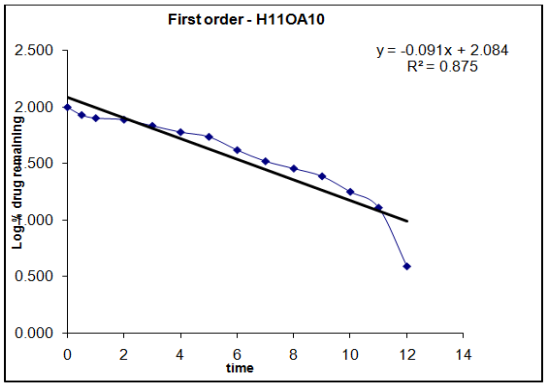

Figure 12: First order release kinetics graph

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

4. Conclusion

The aim of the present study was to develop sustained release formulation of Isoniazide to maintain constant therapeutic levels of the drug for over 12 hrs. Various polymers such as Guar gum, HPMCK100 M,PEG 6000 and Carbopol 934 p were employed as polymers. Isoniazide dose was fixed as 100 mg. Total weight of the tablet was considered as 400 mg. Polymers were used in the concentration of 100, 150 and 200 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. It followed zero order release kinetics mechanism.

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