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Isoniazide Sustained Released Tablet by Using Various Hydrophilic Polymers Formulation and *In-Vitro* Evaluation

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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 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.

Keywords: Isoniazide, Guar gum, HPMC, PEG 6000 and sustained release tablets.

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INTRODUCTION

Oral Controlled Release Drug Delivery Systems

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. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects.

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.

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 allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration.

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.

Advantages of Controlled Drug Delivery Systems:

- Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- More consistent and prolonged therapeutic effect is observed.
- Maximization of efficiency-dose relationship.
- Employ less total drug than that in combined conventional dosage forms.
- Reduction of adverse side effects.
- Minimization of the need for frequent dose intake.
- Improved patient compliance.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Minimize or eliminate local side effects
- Minimize drug accumulation with chronic dosing.

- Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.
- Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects.

Disadvantages of Controlled Drug Delivery Systems:

- Increased variability among dosage units.
- Poor in vitro – in vivo correlation.
- Toxicity due to dose dumping may occur when more than usual fraction is being released.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- More rapid development of tolerance.
- Need for additional patient education and counselling.
- Reduced potential for dose adjustment of drugs normally administered in varying strengths.

Selection of Drug Candidate for Sustained Release Dosage Form

The physico chemical properties of the drug such as pKa, partition coefficient, biological half life, molecular weight, dose of the drug etc., have to be considered before selection.

Characteristics of drugs suitable for formulation as Sustained Release Products

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the gastrointestinal tract.
3. Administered in relatively small doses.
4. Possess good margin of safety.
5. Used for treatment of chronic therapy.

Characteristics of drugs unsuitable for formulation as Sustained Release Products

1. Not effectively absorbed in the lower intestine (Riboflavin).
2. Absorbed and excreted rapidly i.e. short biological half lives, less than one hour (Penicillin G, Furosemide).
3. Long biological half lives greater than 12 hours (Diazepam, Phenytoin).
4. Large doses required, 1gm (Sulphonamides)
5. Drugs with low therapeutic index (Phenobarbital, Digoxin).
6. Precise dosage titrated to individuals required (anticoagulants)
7. No clear advantage for sustained release formulation (griseofulvin)

Types of Oral Controlled Release Drug Delivery Systems

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug.

- Dissolution controlled release systems
- Diffusion controlled release systems
- Diffusion and dissolution systems
- Osmotically controlled release systems
- **Gastroretentive drug delivery systems**
- Electrically stimulated release devices
- Ion-exchange resins

MATERIALS AND METHODOLOGY

Isoniazide, Guargum, Carbopol, HPMC, MCC pH 102, Magnesium stearate, Talc.

Analytical method development:

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.

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 with 100ml of 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 5,10,15,20,25,30,35 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 determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

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 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.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r \quad \tan \theta = \text{Angle of repose}$$

h = Height of the cone , r = Radius of the cone base

Table 1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm³. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, V_o, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where,

M = weight of sample

V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

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

Where,

b = Bulk Density

Tap = Tapped Density

6.3. 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 600mg

Procedure:

- 1) Isoniazide and all other ingredients were individually passed through sieve no \neq 60.
- 2) All the ingredients were mixed thoroughly by triturating up to 15 min.
- 3) The powder mixture was lubricated with talc.
- 4) The tablets were prepared by using direct compression method.

Table 2: Formulation composition for tablets

Formulation No.	Isoniazide	Guar Gum	HPMC K100M	PEG 6000	Carbpol 934	Mag. Stearate	Talc	MCC pH102
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

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.

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 determining 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.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Table 3: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W1-W2) / W] \times 100$$

Where,

W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

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 Meloxicam 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.

In vitro* drug release studies*Dissolution parameters:**

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl , p H 6.8 Phosphate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12

Temperature -- $37^{\circ}\text{c} \pm 0.5^{\circ}\text{c}$

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

Procedure:

900ml Of 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 $37^{\circ}\text{c} \pm 0.5^{\circ}\text{c}$. 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.

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 are fitted to the following equation.

$$F = K_0 t$$

Where, ‘F’ is the drug release at time ‘t’, and ‘K₀’ 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

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

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.

$$F = k t^{1/2}$$

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 transport), $n=1$; and for supercase II transport, $n > 1$. In this model, a plot of $\log (M_t / M_\infty)$ versus $\log (\text{time})$ 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 extended release tablets of Isoniazide using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical Method

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

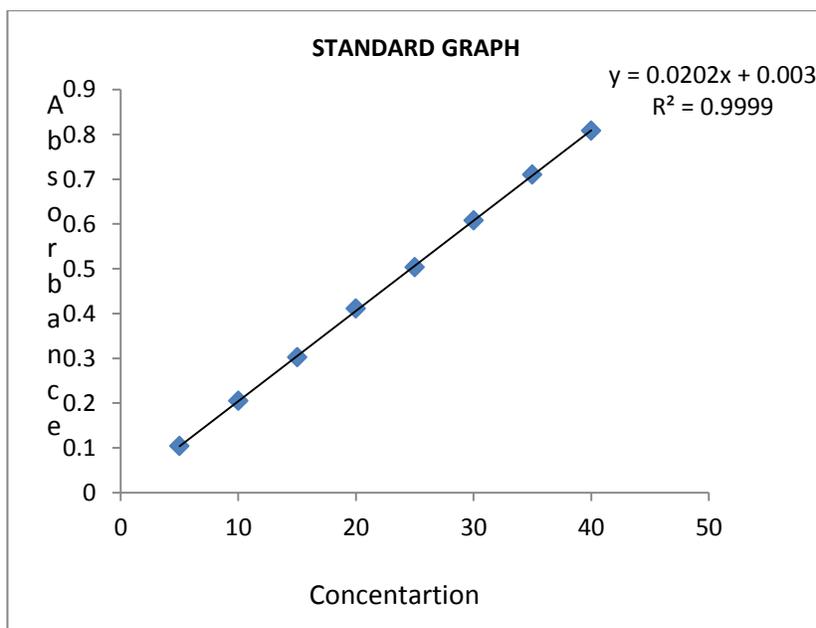


Figure 1: Standard graph of Isoniazide in 0.1N HCl

Table 4: Observations for graph of Isoniazide in 0.1N HCl (256nm)

Concentration[$\mu\text{g/l}$]	Absorbance
5	0.104
10	0.205
15	0.302
20	0.411
25	0.503
30	0.608
35	0.710
40	0.808

Table 5: Observations for graph of Isoniazide in p H 6.8 phosphate buffer (260nm)

Concentration[$\mu\text{g/l}$]	Absorbance
5	0.098
10	0.195
15	0.256
20	0.392
25	0.490
30	0.595
35	0.690
40	0.776

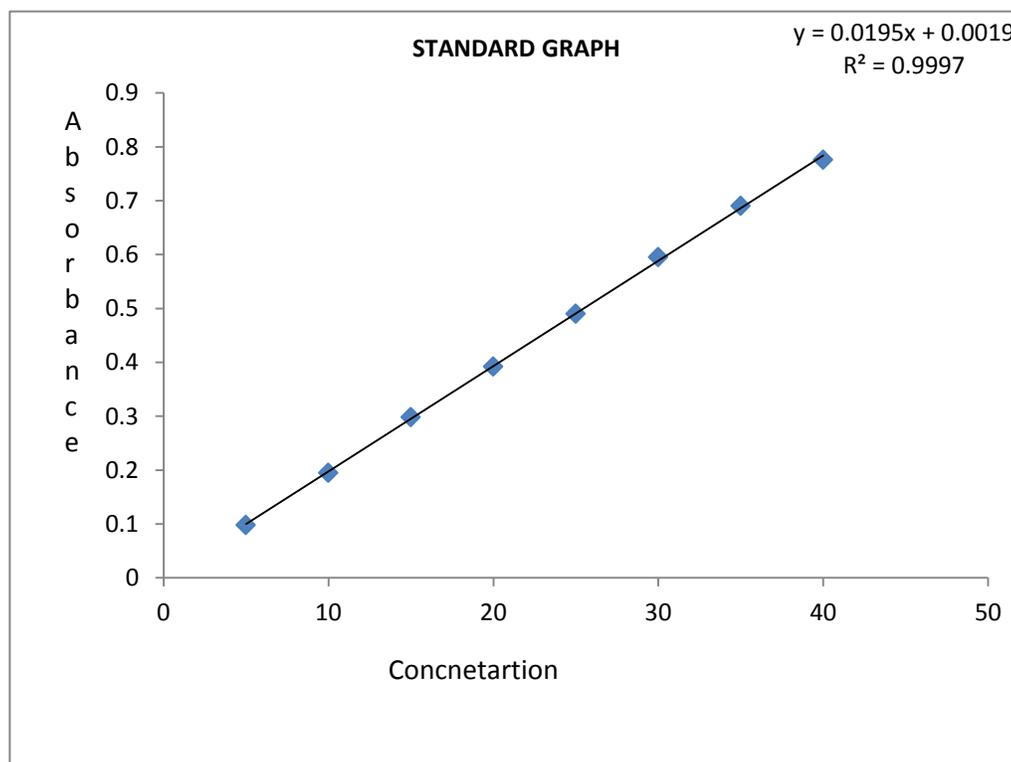
**Figure 2: Standard graph of Isoniazide p H 6.8 phosphate buffer (260nm)****Preformulation parameters of powder blend**

Table 6: Pre-formulation parameters of Core 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	0.52±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

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 7: Invitro quality control parameters for tablets

Formulation codes	Weight variation(mg)	Hardness (kg/cm ²)	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

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.

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

***In-Vitro* Drug Release Studies**

Table 8: Dissolution Data of Isoniazide Tablets Prepared With Guar gum In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	25.5	20.1	16.4	17.25	16.42	14.62	10.4	9.4	8.5	5.12	25.54	3.22
1	46.7	39.4	26.7	38.26	25.73	19.86	16.5	15.6	14.5	9.14	39.66	7.28
2	76.5	55.3	34.6	54.16	36.63	22.35	28.6	21.4	18.4	15.22	54.17	11.24
3	98.4	75.3	42.4	72.01	45.04	31.45	39.5	36.7	23.4	22.74	75.21	15.26
4		87.3	55.4	88.26	58.25	39.80	48.5	42.4	28.2	30.44	86.21	24.28
5		99.4	67.4	97.10	65.33	45.25	59.4	49.6	34.8	39.64	98.33	34.16
6			85.4		76.41	58.24	69.2	55.3	40.2	45.78		39.54
7			91.5		84.84	66.73	74.5	60.3	44.8	52.99		42.15
8			97.3		97.80	71.34	82.3	72.8	50.4	60.14		56.24
9						75.52	87.78	83.52	63.34	65.12		59.54
10						82.17	98.78	88.65	69.27	71.46		64.16
11						87.10		96.56	74.86	79.44		69.18
12						96.10			79.97	82.14		70.21

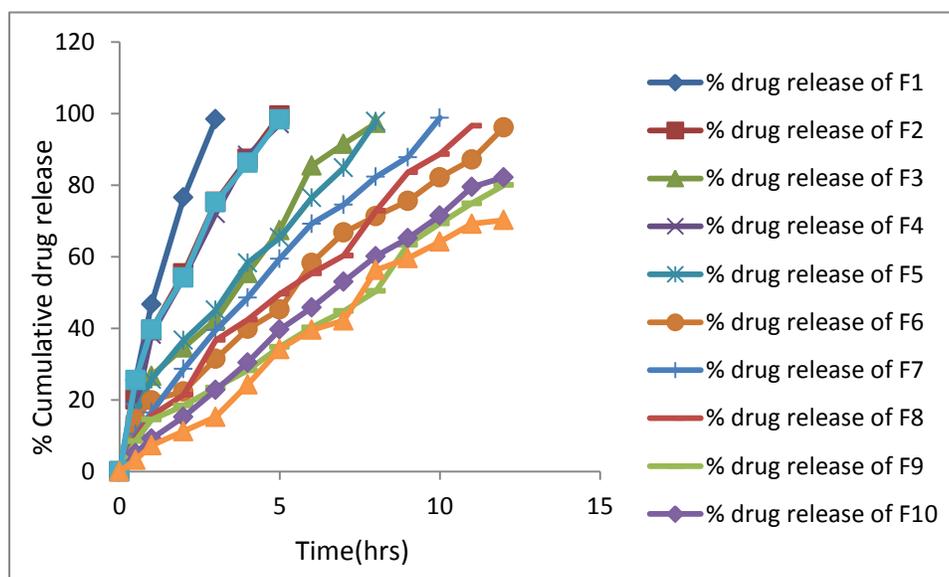


Figure 3: Dissolution profile of Isoniazid .

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.

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

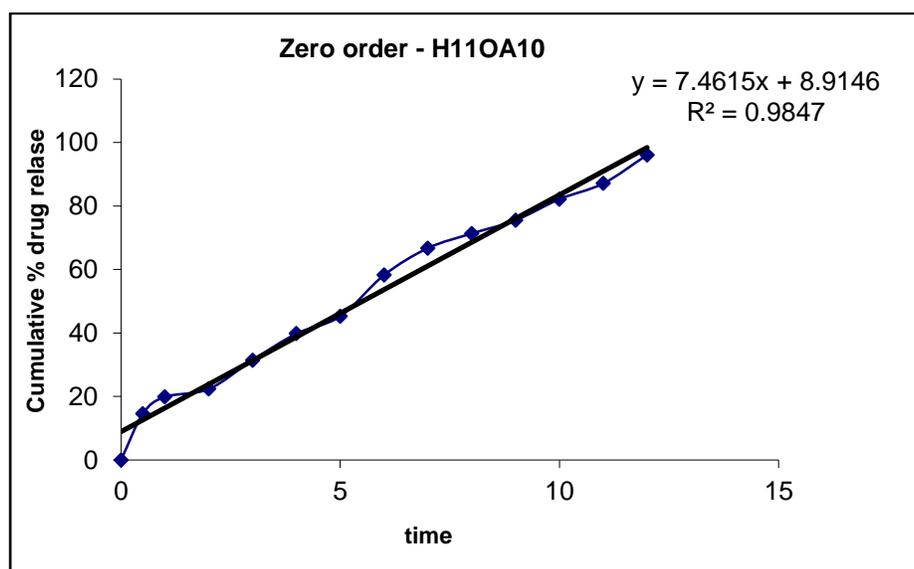


Figure 4: zero order release kinetics graph

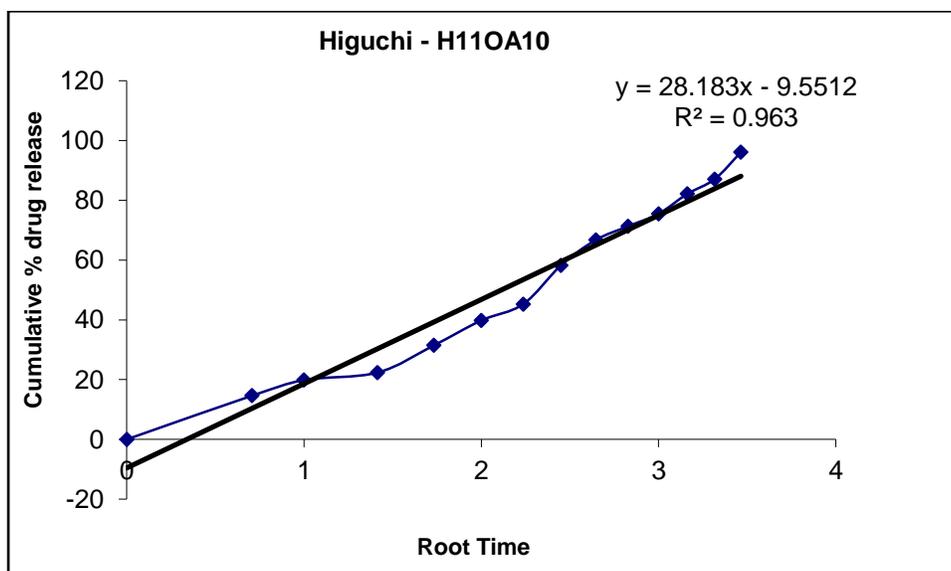


Figure 5: Higuchi release kinetics graph

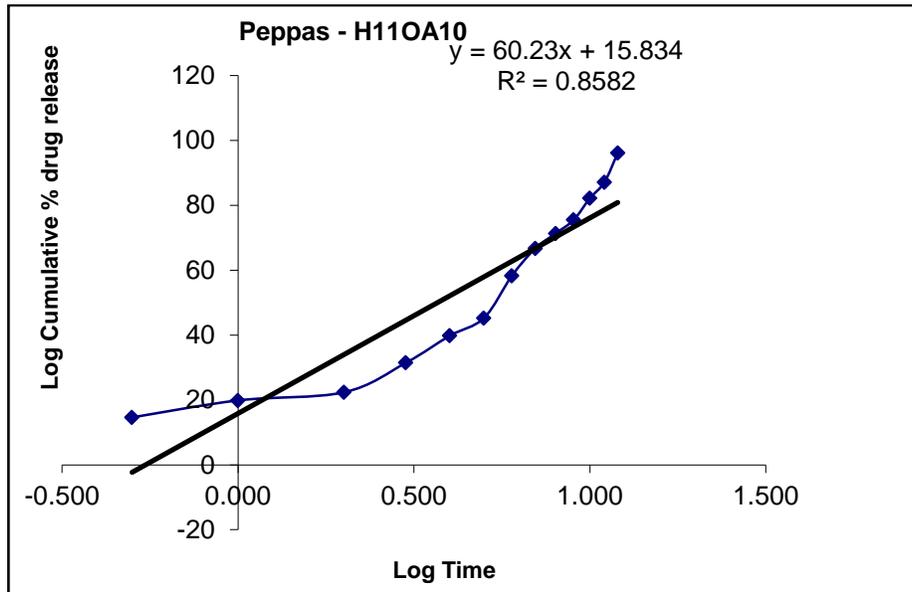


Figure 6: Kars mayer peppas graph

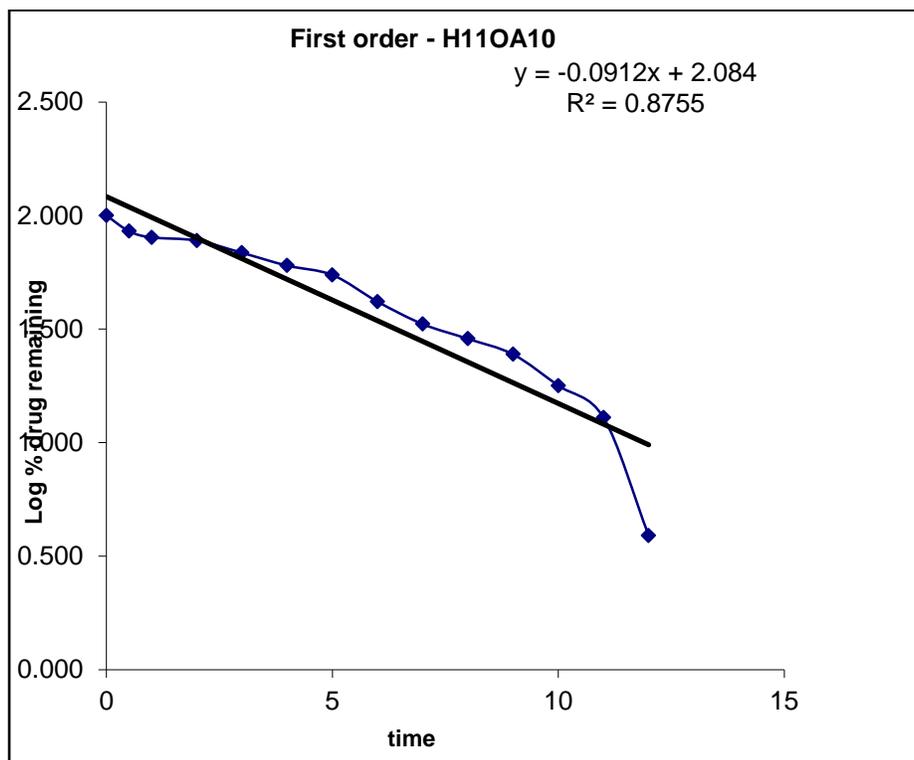


Figure 7: First order release kinetics graph

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 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.

REFERENCE

1. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Pg 515 Fifth Edition, 2004
2. Chien Y.W., Controlled- and modulated-release drug-delivery systems. Encyclopedia of pharmaceutical technology. New York, Dekker, pgs 281-313, 1992.
3. J. R. Robinson, S. P. Eriksen, Theoretical formulation of sustained-release dosage forms. *J Pharm Sci.* 1966
4. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pg 505 Fourth Edition, 2002
5. Leon Lachman, The Theory and Practice of Industrial Pharmacy, Sustained Release Dosage Forms, pgs 430-431, Third Edition, 1987
6. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pgs 505-506 Fourth Edition, 2002
7. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pgs 507-508 Fourth Edition, 2002
8. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pgs 510-511 Fourth Edition, 2002
9. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Pg 535 Fifth Edition, 2004
10. <http://www.pharmainfo.net/reviews/floating-drug-delivery-systemsan-approach-gastro-retention>
11. <http://www.initium.demon.co.uk/relick.htm>
12. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Pg 534 Fifth Edition, 2004

13. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pg 513 Fourth Edition, 2002

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