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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF ISONIAZID

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ABSTRACT

Isoniazid is an antitubercular, with half life of 1.5-4 hours and requires multiple daily doses to maintain adequate plasma concentration. Various formulations of sustained release tablets of isoniazid were developed using various polymers Guargum, Carbopol, TragacanthGum and PEG-6000, in different proportion and combinations by direct compression technique, Bulk density, tapped density, compressibility index, and Hausner ratio before being punched as tablets. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and or standard references. Results of in vitro release profile indicated that formulation (F2) was the most promising formulation as the extent of drug release from this formulation was high as compared to other formulations. It was observed that tablets of batch F2 followed the Zero order release profiles. From the above results and discussion it is concluded that formulation of sustained release tablet of Isoniazid containing Guar gum (1.5%), Batch F2 can be taken as an ideal or optimized formulation of sustained release tablets for 12 hour release as it fulfills all the requirements for sustained release tablet.

KEY WORDS: Isoniazid, Lactose, Starch, Talc, Guargum, TragacanthGum.

INTRODUCTION [1]

Among the drugs that are administered orally, solid dosage form represents the preferred class of product. Solid dosage form provides best protection to the drug against temperature, humidity, oxygen, light and stress during transportation and also ensures accuracy of dosage, compactness, portability, blandness of taste, and ease of administration Tablets are defined as solid dosage forms containing drug substance generally with suitable diluents and prepared by either compression or molding methods. Tablets remain popular as a dosage form because of the advantages afforded, both to the manufacture (e.g. simplicity and economy of the preparation, stability, and convenience in packing, shipping and dispensing) and the patient. Because of their composition, method of manufacture or intended use, tablets prevents a variety of characteristics and consequently there are several categories of tablets. Although the basic medicinal approach for their manufacture has remained the same, tablet technology has undergone great improvement. Efforts are being made continually to understand more clearly the physical characteristic of powder compaction and the factors affecting the availability of the drug substance from the dosage form after oral administration. Tabletting equipment continues to improve in both production speed and the uniformity of the tablets compressed.

POTENTIAL ADVANTAGE OF SUSTAINED RELEASE DOSAGE FORM: [2]

1] Patient compliance:

Lack of compliance is generally observed with term treatment of chronic disease, as success of drug therapy depends upon the ability of patients to comply with the regimen. Patient's compliance is affected by a combination of several factors, like awareness of disease process, patient's faith in therapy, his understanding of the need to adhere to a strict treatment schedule. Also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and systemic side effect of the dosage form.The problem of lack of patient compliance can be resolved to some extent by administration sustained release drug delivery system.

2] Reduced 'see-saw' fluctuation:

Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate often results in 'see-saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitude of these fluctuations depends on drug kinetics such as the rate of absorption, distribution, and dosing

interval. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half lives of less than four hours, since prescribed dosing interval are rarely less than four hours. A well-designed sustained release drug delivery system can significantly reduced the frequency of drug dosing and also maintain a steady drug concentration in blood circulation and target tissue cells.

3] Reduced total dose:

Sustained release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy

Challenges-[3]

1) Dose dumping:

Dose dumping is a phenomenon where by relatively large quantities of drug in a sustained release formulation is rapidly released, introducing potential toxic quantities of drug into the systemic circulation. Dose dumping can lead to facilities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital.

2] Limited choice of selecting desired dose in the unit:

in conventional dosage forms, dose adjustment are much simpler e.g. tablet can be divided into two fractions, in case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

3] Poor In vitro-In vivo correlation:

In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called 'Absorption window' becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in vitro release characteristics.

MATRIX SYSTEM: [4]

The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved

or dispersed in a resistant supports to disintegration. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following must be considered:

a. The chemical nature of support (generally, the support are formed by polymeric net)
b. The physical state of drug (dispersed under molecular or particulate form or both)
c. The matrix shape and alteration in volume as a function of time.
d. The route of administration (oral administration remains the most widely used but other routes are adaptable)
e. The release kinetic model.

THE CLASSIFICATION OF MATRIX SYSTEM:

Mineral matrix:

Drug retained in the support.

Drug adsorbed on the support.

Lipid matrix:

Delivery by diffusion.

Delivery by surface erosion

Hydrophilic matrix:

Unlimited swelling, delivery by diffusion.

Limited swelling controlled delivery through swelling

Inert matrix:

Controlled delivery by diffusion

Biodegradable matrix:

Non-Lipid.

MECHANISMS OF DRUG RELEASE FROM MATRIX SYSTEM[11, 12]

The release of drug from controlled devices is via dissolution of the matrix or diffusion of drug through the matrix or a combination of the two mechanisms.

Dissolution controlled systems

A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water-soluble. This can be done by:

- Preparing an appropriate salt or derivative
- Coating the drug with a slowly dissolving material – encapsulation dissolution control
- Incorporating the drug into a tablet with a slowly dissolving carrier – matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time).

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid tablet is the rate-determining step. The dissolution process at steady-state is described by the Noyes-Whitney equation:

$$Dc/dt = k_D A (C_s - C) = D/hA (C_s - C)$$

dC - dissolution rate

kd - the dissolution rate constant (equivalent to the diffusion coefficient Divided by the thickness of the diffusion layer D/h)

D - Diffusion coefficient

Cs - saturation solubility of the solid

C - Concentration of solute in the bulk solution

Equation 1 predicts that the rate of release can be constant only if the following parameters are held constant: surface area, diffusion coefficient and diffusion layer thickness and concentration difference. However, under normal conditions, it is unlikely that these parameters will remain constant, especially surface area, and this is the case for combination diffusion and dissolution systems.

MATERIALS AND METHODS[5-8]

Table-1:

S. No.	Name	Manufacturer
1.	Isoniazid	Central drug research institute, Lucknow.
2.	Guar gum	Loba chemicals Pvt. Ltd., Mumbai
3.	Carbopol	Burzin and Leones Pvt. Ltd., Mumbai
4	Tragacanth gum	Bombay research labs,Pune
5.	PEG-6000	Sd fine-chemicals limited Bombay
6.	Potassium dihydrogen orthophosphate	Ranbaxy Fine Chemicals Ltd. Mohali
7.	Sodium hydroxide	Qualigens Fine Chemicals Mumbai.
8.	Hydrochloric acid	Qualigens Fine Chemicals, Mumbai.
9.	Magnesium Stearate	S. D Fine Chem. Ltd., Mumbai.
10.	Talc	Nice Chemicals Pvt. Ltd., Cochin.
11	Lactose	Nice Chemicals Pvt. Ltd., Cochin.
12	Starch	Loba chemicals Pvt. Ltd., Mumbai

Table-2:

Sr. no.	Name of Equipment	Manufacturer
1.	Weighing balance (HR-200)	AND company Ltd. Japan
2.	pH meter(L1-120)	Elico Ltd., Hyderabad.
3.	Pestle Mortar	Narang Scientific Works Pvt. Ltd., N. Delhi.
4.	Hot air oven	LABCO, Ambala.
5.	Tablet punching machine	Spinex Pvt. Ltd.
6.	Hardness tester	JSGW Pvt. Ltd. , Ambala
7.	Friability tester	Prolific Engg. Noida.
8.	U.V.-Vis-NIR spectrophotometer(Cary5000)	Cary varian Pvt. Ltd. Australia
9.	Disintegrator	TA Instruments New castle DE, USA
10.	Dissolution apparatus	Hi-media Laboratories Pvt. Ltd.,Mumbai
11.	Thickness tester	Electro lab Pvt. Ltd., Mumbai
12.	Vernier caliper	Decibel Instruments, Chandigarh.

FORMULATION OF ISONIAZID MATRIX TABLET

Each quantity mentioned will be taken in mgs

Total weight of the tablet = 350mg

Each tablet contains = 100mg of the drug

FORMULATION OF MATRIX TABLETS OF ISONIAZID[9-13]

All the ingredients are weighed according to the working formula and matrix tablets of isoniazid were prepared by direct compression method. Formulation of isoniazid matrix tablets quantity are listed in Table no;-3

EVALUATION OF TABLET[14-20]

All the prepared Sustained release tablets were evaluated for following official and unofficial parameters.

- Weight Variation
- Thickness
- Hardness Test
- Friability Test
- Drug content
- Dissolution Study

WEIGHT VARIATION:

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in

Table No-3:

Ingredients Quantity in [mg]	**F1**	**F 2**	**F3**	**F 4**	**F 5**	**F 6**	**F 7**	**F 8**	**F 9**	**F10**	**F11**	**F 12**
Drug	100	100	100	100	100	100	100	100	100	100	100	100
Guar gum	100	150	200	-	-	-	-	-	-	-	-	-
Tragacanth- gum	-	-	-	100	150	200	-	-	-	-	-	-
PEG-6000	-	-	-	-	-	-	100	150	200	-	-	-
Carbopol-934p	-	-	-	-	-	-	-	-	-	100	150	200
Magnesium-Stearate	7	7	7	7	7	7	7	7	7	7	7	7
Talc	7	7	7	7	7	7	7	7	7	7	7	7
Starch	21	21	21	21	21	21	21	21	21	21	21	21
Compressible Lactose	115	65	15	115	65	15	115	65	15	115	65	15

THICKNESS

Twenty tablets were randomly selected from each batch and there thickness and diameter was measured by using digital vernier caliper.

TABLET HARDNESS

The crushing strength Kg/cm^2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester. The average hardness and standard deviation was determined. The results are shown in Table No.

FRIABILITY:

Method:

Twenty tablets were weighed and placed in the Electro lab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again Table No. 8 The percentage friability was measured using the formula,

$$\% F = \{1-(W_t/W)\} \times 100$$

Where, % F = friability in percentage

W = Initial weight of tablet

W_t = weight of tablets after revolution

CONTENT UNIFORMITY [86]

Transfer one finely powdered tablet to a 500ml volumetric flask with the aid of 200ml of water. Shake by mechanical means for 30min. add water to volume and mix filter and discard with first 20ml of the filtrate dilute a portion of the filtrate quantitatively and step wise if necessary with a 3 in 100 mixture 0.1N HCL and water to obtain a solution containing about 10µg/ml. dissolve an accurately weighed quantity of USPRF in a volume of water corresponding to that used to dissolve a similar amount of Isoniazid from tablet and dilute if necessary with a 3 in 100mix of 0.1n HCl and water to obtain a standard solution having known concentration of about 10µg/ml concomitantly determine the absorbance of both solutions in 1 cm cells at wave length max absorbance at 263nm.suitable spectrophotometer using water as a blank calculate quantity in mg of $C_6H_7N_3O$ in tablet taken.

IN VITRO DISSOLUTION STUDIES[86]

In Vitro dissolution study was carried out using USP I apparatus (basket apparatus) in 900 ml of 0.1 N HCl (pH 1.2), pH 6.8 for 12 hours. The temperature of the dissolution medium was kept at 37± 0.5^{o}C and the basket was set at 50 rpm. 10 ml of sample solution was withdrawn at specified interval of time and filtered through Whatman filter paper. The absorbance of the withdrawn samples was measured at λ_{max} 263 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of Isoniazid prepared in 0.1N HCl (pH 1.2), pH 6.8 at λ max 263 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve. The immediate release part for sustained release Isoniazid was also calculated.

SWELLING INDEX[87]

The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

Method:

For each formulation batch. One tablet was weighed and placed in a Petri plate containing 25ml of 1.2 pH buffer solution. After each interval the tablet was removed from beaker, removes excess of buffer by using filter paper and weighed again up to 12 hours. Swelling index was calculated by using the following formula.

$$\textbf{Swelling index WU} = \left(\frac{W_1 - W_0}{W_0}\right) \times 100$$

Where, Wt = Weight of tablet at time t.

W_0 = Initial weight of tablet

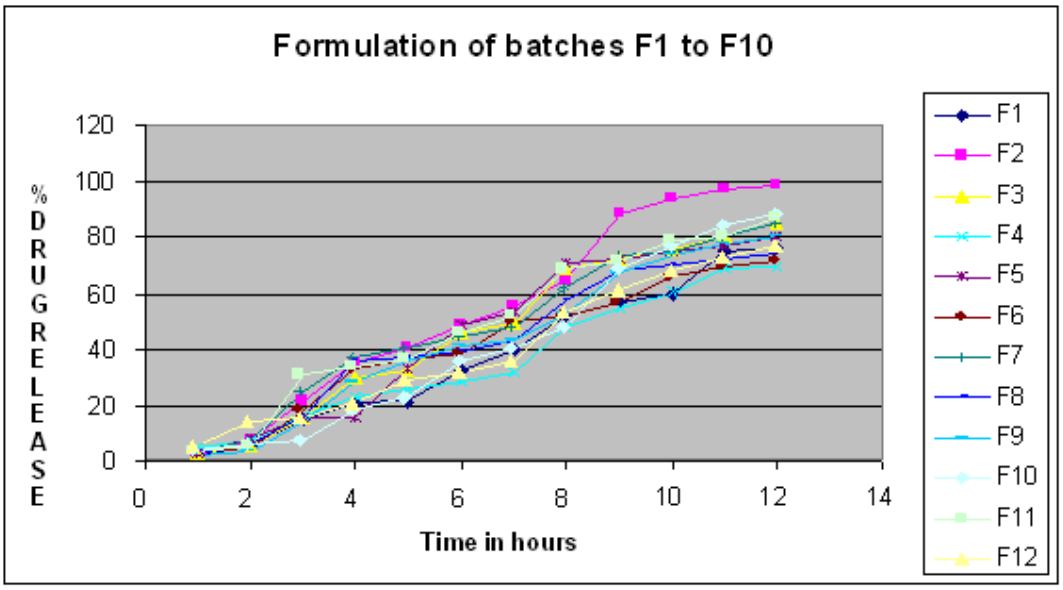
RESULTS

Table No: 4

Time (hrs)	F 1	F 2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	2.37	2.61	2.45	4.66	2.65	3.37	3.66	2.60	2.24	3.98	3.25	5.39
2	5.58	7.63	5.78	7.80	8.30	4.98	7.43	5.86	3.66	6.38	5.18	14.19
3	14.78	21.41	16.03	16.15	15.95	18.64	24.58	16.31	14.66	7.79	30.16	16.03
4	20.53	34.67	29.45	22.86	16.03	32.62	36.80	35.39	28.08	18.72	33.26	20.73
5	21.13	40.17	31.98	22.55	32.66	36.68	40.17	37.00	35.65	22.45	36.56	28.55
6	32.14	48.85	45.76	22.80	48.65	38.37	44.31	39.08	41.06	35.45	46.12	31.86
7	39.89	55.88	49.25	31.78	53.47	50.02	47.81	42.90	43.18	46.62	52.13	36.00
8	52.23	64.72	68.66	48.18	70.91	52.19	61.47	57.89	52.99	48.05	68.66	53.67
9	56.81	88.32	72.32	54.68	72.04	57.01	73.12	68.18	67.01	68.71	71.31	60.79
10	59.66	94.05	75.57	60.22	74.97	65.53	74.73	70.07	73.56	76.62	78.79	67079
11	74.81	97.19	80.35	68.74	.76.74	69.22	80.35	72.04	77.70	84.41	80.01	72.80%
12	75.95	98.87	84.81	69.58	80.27	71.47	84.77	74.29	80.11	88.35	86.78	76.74

Table No: 5

Parameter Batch	Weight Variation (mg)	Hardness (Kg/cm2)*	Friability (%)	Thickness (mm)*	Disintegration Time(sec) *	Drug Content (%)
F 1	350.1	5.51	0.55	4.4	196±	99.50
F 2	348.9	5.80	0.59	4.0	240	98.60
F 3	325.2	5.93	0.61	4.3	210	100.02
F 4	351.4	6.20	0.58	4.1	243	99.59
F 5	349.3	6.11	0.63	4.5	191	99.38
F 6	348.4	6.35	0.76	4.2	200	99.05
F 7	350.7	6.41	0.70	4.6	317	99.60
F 8	351.5	6.44	0.66	4.3	250	102.06
F 9	349.3	6.68	0.53	4.1	213	100.62
F 10	350.1	6.71	0.71	4.2	300	99.50



Dissolution Profile of F1-F12 formulations (1%, 1.5% & 2% of guar gum)

CONCLUSION

Various formulations of sustained release tablets of Isoniazid were developed using various polymers viz, Guar gum, TragacanthGum, PEG-6000 and Carbopol in different proportions and combinations by direct compression technique. The tablets were evaluated for physical characterization, *in vitro* swelling behavior, *in vitro* release study and stability studies. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and/or standard references. Results of in vitro release profile indicated that formulation (F2) was the most promising formulation as the extent of drug release from this formulation was high as compared to other formulations. Results of in vitro swelling study indicate that the formulation F2 was having considerable swelling index. From the above results and discussion it is concluded that formulation of sustained release tablet of Isoniazid containing Guar gum (1.5%),batch F2 can be taken as an ideal or optimized formulation of sustained release tablets for 12 hour release as it fulfills all the requirements for sustained release tablet.

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