Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2014, Volume 2, Issue 4
ISSN:2321–3647(online)

Formulation and Evaluation of Sustained Release Matrix Tablet of Isonizaid by Direct Compression Technique

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ABSTRACT

The objective of the present work was to develop modified release tablets of Isoniazid by using HPMC as a release-controlling agent. The different-viscosity grades of HPMC were used to prepare the matrix tablets. The tablets were prepared by direct compression. The prepared tablets were subjected to physical characterization and *in vitro* drug release studies. The *in vitro* drug release was carried out by using USP apparatus I in 900 ml of acidic dissolution medium (pH 1.2) for 2 h, followed by 900 ml alkaline dissolution medium (pH 6.8) at 50 rpm. The polymer type did not affect the flow of powder blend and crushing strength of Isoniazid tablets. The drug release rate was strongly influenced by the type of polymer and the concentration of polymer. Different proportion of HPMC was associated with decrease in the overall cumulative drug release rate. The initial burst release of Isoniazid was decreased by higher viscosity grade polymer. Thus, we conclude that from among all the developed formulations, F1 formulation sustained the drug release for longer period of time over 12 h when compared to other formulations. So, F1 was selected as best formulation and fulfills all the requirements for sustained release.

Keywords: Direct compression, Isoniazid, Hydroxyl propylmethyl cellulose, In-vitro release studies.

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Received 18 March 2014, Accepted 29 March 2014

Please cite this article in press as: Shibu BS *et al*., Formulation and Evaluation of Sustained Release Matrix Tablet of Isonizaid by Direct Compression Technique. American Journal of Pharmacy & Health Research 2014.

INTRODUCTION

This sustained release dosage forms are becoming popular as these have a number of advantages over conventional dosage frequencies, less fluctuation in circulating blood levels, increased patient compliance and more uniform effect. The main concept of sustained drug delivery system are the use of system and techniques for altering and controlling the absorption, blood levels metabolism, organ distribution and cellular uptake of pharmacologically active agents. The main aim of a sustained or controlled release dosage form is to produce an improved therapy by producing a uniform plasma concentration of drug at steady state and by reducing the ratio of maximum and minimum plasma levels after each dose.

Tuberculosis (TB), a rampant infectious disease, is considered to be the foremost cause of death from a single microorganism. Annually worldwide, of the 8 million people who actively manifest the disease, 3 million die[2] . Chemotherapy of TB is complicated by the need of multi-drug regimens given over a long period. Development of delivery system that releases drug in a sustained manner at therapeutic concentration over a period of time can ensure patient compliance and may also minimize the risk of emergence of drug resistant mutants and potential toxicity.

Isoniazid is a first-line drug recommended by World Health Organization (WHO) for the treatment of tuberculosis. The high solubility in the aqueous medium, shorter half-life (1.5 to 4.5 h) and absorption throughout gastrointestinal tract, indicates that it is a better candidate for sustained drug delivery system. During the last few years, various carrier systems, like micro particles, stealth liposome and microspheres have been developed for the sustained delivery of isoniazid for better chemotherapeutic efficacy against tuberculosis[3,4]. However, these formulations have to be injected either subcutaneously or intravenously. The parenteral route is not suitable for long-term treatment. Hence, there is a need to develop an oral drug delivery system that is convenient for the patient.

Hydroxyl propyl methylcellulose (HPMC), a semi-synthetic derivative of cellulose, is one of the best choices as swellable and hydrophilic polymer. It has been widely used in the formulation of hydrophilic matrices for oral extended release drug delivery due to its key features and advantages including global regulatory acceptance, stability, ease of manufacture, versatility, suitability for various drugs and release profiles, and availability of the polymer [5-9].

MATERIALS AND METHODS

Isoniazid (INH) IP was received as a gift sample from the Madras Pharmaceuticals Pvt. Ltd.

Chennai. Various grades of Hydroxyl propyl methylcellulose (Methocel K4M, Methocel K15M and Methocel K100M) were obtained as gift from Novel therapeutics Pvt. Ltd. Chennai., Dicalcium phosphate; Magnesium Stearate and Aerosil were purchased from Nice Chemicals Pvt. Ltd, Cochin.

Preparation of sustained release matrix tablets:

SR matrix tablets of Isoniazid were prepared by direct compression method using different drug: polymer ratios viz. 1:1, 1:2, 1:3, respectively. Table 2 shows the formulations of matrix tablets. Formulation F1 toF3 contains isoniazid and HPMC K5M while formulations F4 to F6 contain isoniazid along with HPMC K15M and formulations F7 to F9 contain isoniazid along with HPMC K100M SR [10-13]. Twenty tablets were prepared for each formulation. The particles were passed through 40 mesh and properly weighed HPMC K5M/HPMC K15M / HPMC K100M SR, Dicalcium phosphate, Magnesium Stearate, Aerosil and Isoniazid were blended in a laboratory mixture for 10 minutes. Proper attention has been given to ensure thorough mixing and phase homogenization.

Table 1: Formulation of Isoniazid Matrix Tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Isoniazid (mg)	70	70	70	70	70	70	70	70	70
HPMCK4M (mg)	70	140	210	-	-	-	-	-	-
HPMC K15M (mg)	-	-	-	70	140	210	-	-	-
HPMC K100M (mg)	-	-	-	-	-	-	70	140	210
Dicalcium phosphate(DC grade) (mg)	155	85	15	155	85	15	155	85	15
Magnesium Stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total (mg)	300	300	300	300	300	300	300	300	300

Each quantity mentioned will be taken in mgs, Total weight of the tablet = 300mg, Each tablet contains= 70 mg of the drug

EVALUATION OF GRANULES[14, 15]

Bulk Density:

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M/ Vb$$

Where, M is the mass of powder, Vb is the bulk volume of the powder.

Tapped Density (Dt):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where, M is the mass of powder , Vt is the tapped volume of the powder.

Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt is the tapped density of the powder and Db. is the bulk density of the powder.

Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where, Dt is the tapped density, Db is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\tan (\theta) = h / r$$

$$\theta = \tan^{-1} (h / r)$$

Where, *h* = height of pile, R = radius of the base of the pile, θ = angle of repose

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property. The result had shown in table no 2.

EVALUATION OF TABLET[16-20]

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

Weight variation:

Twenty tablets were randomly selected from 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 than two of the individual tablet weights deviate from the average weight by more than the percentage shown in Table No.3 and none deviate by more than twice the percentage shown.

Thickness

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

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 3.

Friability:

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. 3. 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

Uniformity of Content

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 std 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. The result had shown in table 3.

In Vitro Dissolution Studies[20]

In Vitro dissolution study was carried out using USP I apparatus (basket apparatus) in 900 ml of pH 1.2 (0.1 N HCl) solution for first 2 h and pH 6.8 buffer (Phosphate buffer) solution for additional 10 h. The baskets were rotated at 50 rpm and the dissolution media were maintained at 37± 0.5^{o}C. 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 buffer (Phosphate buffer) 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. The result had shown in table 4 and Figure 1.

Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifies the length of study and storage conditions.

Long term testing - 25 ºc ±2˚c / 60%RH±5% for 12 months.

Accelerated testing - 42˚c ±2˚c / 75% RH±5% for 6 months.

Procedure:

In the present study stability studies were carried out for a specified time period up to the 30 days for selected formulations.

The selected formulations were analyzed for following parameters:

Physical evaluation

Appearance:

The selected samples were checked for any change in colour every week.

Hardness:

The selected samples were tested for hardness every week.

Chemical evaluation:

Drug content:

The selected formulations were checked for drug content. The selected formulations were subjected to drug release studies.

RESULTS AND DISCUSSION

This study deals with the investigations carried out with the objective of developing oral sustained release formulations through matrix tablets for the widely used anti-tuberculosis (TB) drug. The present study was undertaken with an aim to formulate and evaluate Isoniazid sustained release tablets, prepared by direct compression method by using different grades of HPMC (HPMC K4M, HPMC K15M, and HPMC K100M).

Table 2: Pre compression Parameter of Isoniazid Sustain Release Granules

Formulation	Bulk Density	Tapped Density	Compressibility Index	Hausner's Ratio	Angle of repose (Degree)
F1	0.51	0.62	17.74	1.21	22.5
F2	0.53	0.63	15.87	1.18	26.4
F3	0.55	0.63	12.69	1.14	25.3
F4	0.53	0.64	17.18	1.20	23.2
F5	0.53	0.63	15.87	1.18	24.6
F6	0.52	0.63	17.46	1.21	25.3
F7	0.52	0.64	18.75	1.23	23.5
F8	0.53	0.63	15.87	1.18	24.1
F9	0.36	0.42	15.9	1.17	25.1

The powder blend was evaluated for the physical properties such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The angle of repose was found to be between 22.5 to 26.4, this indicates passable flowability. The percentage compressibility index and Hausner's ratio were within the limits.

Table 3: Physicochemical Evaluation of Matrix Tablet

Formulations	Weight Variation (mg)	Hardness (Kg/cm2)	Friability (%)	Thickness (mm)	Disintegration Time(sec)	Drug Content (%)
F1	350.1	5.51	0.55	4.4	196	99.50
F2	348.9	5.80	0.59	4.0	240	98.60
F3	325.2	5.93	0.61	4.3	210	100.02
F4	351.4	6.20	0.58	4.1	243	99.59
F5	349.3	6.11	0.63	4.5	191	98.38
F6	348.4	6.35	0.76	4.2	200	99.05
F7	350.7	6.41	0.70	4.6	237	102.06
F8	351.5	6.44	0.66	4.3	220	99. 60
F9	349.3	6.68	0.53	4.1	213	100.62

The prepared tablets were evaluated for hardness, thickness, friability, drug content, weight variation. The drug content was found to be within the acceptable limits (98 to100).The results of

evaluation of tablet showed that the dimensions, hardness, friability, and weight variation were found to be within the specified limit.

Table 4: Dissolution Profile of F1 to F9 formulations

Serial no:	Time (hrs)	Cumulative % Drug Released								
		F1 (1:1)	F2 (1:2)	F3 (1:3)	F4 (1:1)	F5 (1:2)	F6 (1:3)	F7 (1:1)	F8 (1:2)	F9 (1:3)
1	0.5	3.06	2.8	2.79	2.42	2.05	2.05	2.28	1.89	1.54
2	1	7.93	3.63	3.45	4.92	3.25	3.49	5.01	3.32	2.97
3	1.5	12.61	7.6	6.51	10.06	6.32	6.09	8.66	4.31	3.76
4	2	16.53	10.46	9.25	14.65	12.31	8.19	11.96	7.65	5.96
5	3	40.57	26.37	20.92	25.82	20.95	20.65	21.79	13.84	11.61
6	4	54.35	39.81	31.86	36.31	35.86	25.12	30.94	24.83	20.88
7	5	65.91	47.58	43.33	47	46.33	33.68	45.61	35.41	31.86
8	6	72.86	56.33	48.94	54.37	54.96	47.44	50.42	47.12	41.72
9	7	79.09	65.21	58.73	65.11	67.53	56.51	58.84	56.62	48.72
10	8	88.25	74.95	63.81	75.56	72.55	65.87	65.24	64.06	56.93
11	9	90.51	83.93	72.73	82.57	76.43	72.73	70.09	69.73	62.09
12	10	94.35	86.44	78.79	86.97	79.92	75.61	74.65	71.2	66.56
13	11	97.14	90.51	82.06	88.19	81.17	77.08	80.44	75.56	70.33
14	12	98.85	92.91	86.62	90.85	82.91	80.87	82.35	79.31	72.73

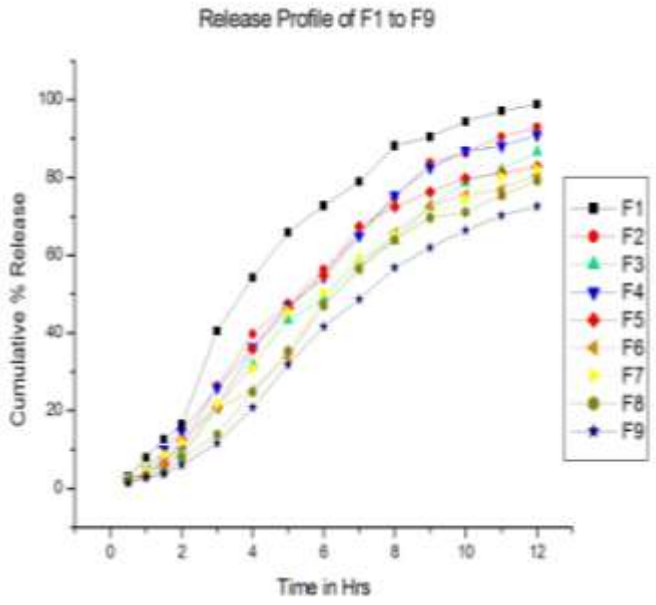

Figure 1: Release profile of F1 to F9

From *in-vitro* drug dissolution profile of Isoniazid matrix tablet, it was found that 16.53% of the drug was released till 2 h from F1 formulation (Drug: HPMC 1:1). After 2-8 h more than 60-80% of the drug was released. After 8 h the release rate was decreased slightly and a sustained release

pattern was observed for 12 h. Isoniazid release was controlled by hydrophilic matrix of HPMC for 12 h. It was observed that formulation with the drug polymer ratio 1:1 (F1, F4, F7) showed high drug release rates in the range of 98.85 % to 82.35% when compared to 1:2 ratio (F2, F5, F8) which showed a drug release rates from 92.91% to79.31% and those of 1:3 ratio (F3, F6, F9) which showed a drug release rates in the range of 86.62 % to 72.73 % over a period of 12 h. The rate of drug release from the selected polymers were found to decrease in the following order HPMC K4M > HPMC K15M > HPMC K100M.

Among the three grades of polymer used the tablets prepared with lower viscosity grade i.e. HPMC K4M, have shown drug release rate (98.85% to 86.62 %) and the higher viscosity grade polymers i.e. HPMC K15M (90.85 % to 80.87%) and HPMC K100M (82.35% to 72.73%). But the much difference was not found in the drug release profiles of tablets prepared with HPMC K4M and HPMCK15M.

Different proportion of HPMC was associated with decrease in the overall cumulative drug release rate. The higher viscosity polymer had been seen to inhibit the initial burst release of Isoniazid. Thus, we conclude that from among all the developed formulations, F1 formulation sustained the drug release for longer period of time over 12 h when compared to other formulations. So, F1 was selected as best formulation.

Table 5: Physico chemical evaluation for most satisfactory formulation during stability studies

	Drug content (%)	Hardness (Kg/cm^2)	Friability (%)
After one month	99.68	5.49	0.55

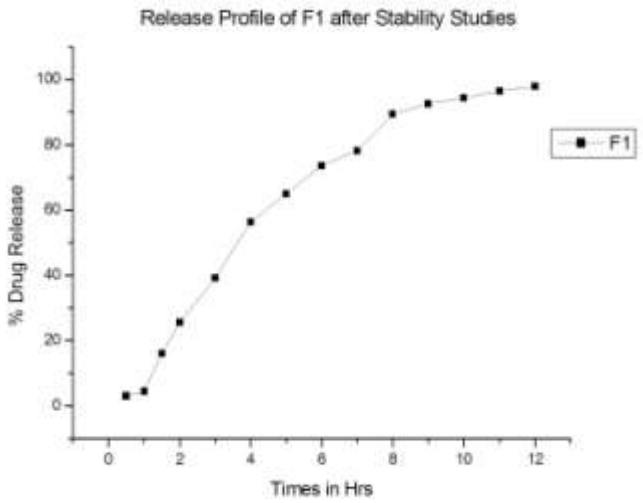

Figure 2: Release profile of F1 after stability studies

The selected formulation was evaluated for accelerated stability studies. The formulation were stored at 40^{o} C at 75% RH for 1 month and analyzed for their physical parameters, drug content and in vitro dissolution studies. After storage the formulation was subjected to drug content, hardness, friability and *in vitro* dissolution studies and there was no significant change in the results.

CONCLUSION:

It is concluded that the formulated matrix tablets of Isoniazid using different grades of HPMC were capable of exhibiting sustained release properties. They are thus capable of reducing the dose intake, minimize the blood level oscillations, dose-related adverse effects and cost thus ultimately improve the patient compliance.

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