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Formulation and evaluation of sustained release matrix tablets of Isoniazid

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ABSTRACT

Sustained release tablets of isoniazid were fabricated using guar gum and carbapol, Tragacanth Gum and PEG-6000, in different proportion and combinations by direct compression technique, Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. The tablets were evaluated for physical characteristic like hardness, weight variation, friability, and drug content. 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. 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.

Keywords: Isoniazid, Carbapol, Guargum, Tragacanthum, Sustained release.

INTRODUCTION

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Regular research is going on in field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration[1]. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage

forms Guar gum a polysaccharide derivative with glycoside linkage has been used as matrix former for controlled release of diltiazem[2]. Tragacanth gum, a high molecular weight polysaccharide gum, it contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt[3]. Isoniazid is a first line drug in treatment of tuberculosis and it is a prodrug and must be activated by bacterial catalyse. It is activated by catelase-peroxidase enzyme katG to form isonicotinic acyl anion or radical. These forms will then react with a NADH radical or anion to form isonicotinic acyl-NADH complex. This complex will bind tightly to ketoenoylreductase known as inhA and prevents access of the natural enoyl-AcpM subustrate[4]. This mechanism inhibits the synthesis of mycolic acid in the mycobacterial cell wall. Isoniazid is bactericidal to rapidly-dividing mycobacteria, but is bacteriostatic if the mycobacterium is slow-growing[5]. The present investigation is aimed to formulate the sustained release matrix tablet of isoniazid with guar gum, tragacanth and carbopol.

MATERIAL AND METHODS:

Isoniazid was obtained as gift sample from Central drug research institute, Lucknow. And Pharmacopoeial grade Guar gum from Loba chemicals Pvt. Ltd., Mumbai. Carbopol from Burzin and Leones Pvt. Ltd., Mumbai, Tragacanth gum from Bombay research labs, Pune.PEG-6000 from Sd fine-chemicals limited Bombay.

Preparation of SR matrix tablets:

SR matrix tablets of isoniazid were prepared by using different drug: polymer ratios viz. 1:1, 1:1.5, 1:2 for P1,P2, P3, P4, 1:1, 1:1.5, 1:2 for G1, G2, G3, G4 and 1:1,1:1.5,1:2 for P1, P2, P3, P4 respectively were used as matrix forming material, while lactose was used as diluent, Magnesium stearate was incorporated as Lubricant. All ingredients were passed through a #100 sieve, weighed, and blended. The lubricated formulations were compressed by a direct compression technique, using 12 mm flat faced punches.

Table no 1: Formulation of isoniazid matrix tablet

Batch > ingredients	**F1**	**F 2**	**F3**	**F 4**	**F 5**	**F 6**	**F 7**	**F 8**	**F 9**	**F10**	**F11**	**F12**
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

Each quantity mentioned will be taken in mgs
Total weight of the tablet = 350mg
Each tablet contains = 100mg of the drug

Evaluation of granules[6]

Angle of repose:

Angle of repose was determined using funnel method[6].The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap(r) was measured and the angle of repose (Θ) was calculated using the formula[7].

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

Bulk density:

Apparent bulk density (p_b) was determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula[7].

$p_b = M/ V_b$

Tapped density:

The measuring cylinder containing a known mass of blend was tapped for a fixed time.The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (p_t)[6] was calculated by using formula.

$p_t = M/ V_t$

Compressibility index:

The simplest way for measuring of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I)[6] which is calculated as follows.

$I = (V_0 - V_t/ V_0)\ 100$

Where, vo is the bulk volume and vt is tapped volume. The value below 15% indicates a powder with usually give rise to good flow characteristics, where as above 25% indicates poor flowability.

Loss on drying:

Determination of loss on drying of granules is important drying time during granulation was optimized depending LOD value. LOD of each batches were tested at 105^{o}c for 2.5 minutes by using “Sartorius” electronic LOD apparatus.

Table no 2: Evaluation of tablets blends

Parameter Batch	Bulk Density	Tapped Density	Carrs Index	Hausners Ratio	Angle Of Repose(degree)
F 1	0.442	0.638	7.22	1.08	18.10±0.03
F 2	0.522	0.513	7.29	1.10	18.19±0.06
F 3	0.510	0.601	7.31	1.04	19.51±0.057
F 4	0.521	0.711	7.63	1.06	20.33±0.042
F 5	0.560	0.730	7.59	1.14	21.494±0.02
F 6	0.493	0.513	7.86	1.09	21.11±0.026
F 7	0.591	0.509	8.30	1.12	23.962±0.01
F 8	0.601	0.600	8.14	1.15	18.21±0.02
F 9	0.630	0.609	9.11	1.11	24.14±0.042
F 10	0.616	0.510	11.62	1.00	24.18±0.41
F 11	0.592	0.611	13.60	1.18	20.64±0.026
F 12	0.660	0.731	13.11	1.13	24.13±0.042

Evaluation of tablets[8]:

Weight variation:

Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and were compared with average weight.

Friability:

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were deducted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$F = (1-W_0/W)\ 100$

Where, W_0 is weight of the tablets before and W is weight of the tablets after test.

Hardness:

Hardness was measured using Monsanto tablet hardness tester.

Thickness:

Ten tablets were taken from each formulation and their thickness was measured using digital Vernier calipers (Mitutoyo corp, Kawasaki,Japan).

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 filterate dilute a portion of the filterate 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 taken in 1 cm cells at wave length max absorbance at 263nm.

Table no 3: Evaluation of prepared tablets

Parameter Batch	Thickness (mm)*	Disintegration Time(sec)*	Weight Variation (mg)	Hardness (Kg/cm2)*	Friability (%)	Drug Content (%)
F 1	4.4	196	350.1	5.51	0.55	99.50
F 2	4.0	240	348.9	5.80	0.59	98.60
F 3	4.3	210	325.2	5.93	0.61	100.02
F 4	4.1	243	351.4	6.20	0.58	99.59
F 5	4.5	191	349.3	6.11	0.63	99.38
F 6	4.2	200	348.4	6.35	0.76	99.05
F 7	4.6	317	350.7	6.41	0.70	99.60
F 8	4.3	250	351.5	6.44	0.66	102.06
F 9	4.1	213	349.3	6.68	0.53	100.62
F 10	4.2	300	350.1	6.71	0.71	99.50
F 11	4.6	144	353.1	6.89	0.69	100.02
F 12	4.1	231	349.2	6.91	0.68	101.01

In vitro dissolution studies:

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. 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.

Table no 4: Dissolution Profile of F1, F2 & F3 formulations (1%, 1.5% & 2% of guar gum) & Dissolution Profile of F4, F5 & F6 formulations (1%, 1.5% & 2% of tragacanthGum)

Serial no.	Time (hrs)	%release F 1	%release F 2	%release F3	%release F 4	%release F 5	%release F 6
1	1	2.37	2.61	2.45	4.66	2.65	3.37
2	2	5.58	7.63	5.78	7.80	8.30	4.98
3	3	14.78	21.41	16.03	16.15	15.95	18.64
4	4	20.53	34.67	29.45	22.86	16.03	32.62
5	5	21.13	40.17	31.98	22.55	32.66	36.68
6	6	32.14	48.85	45.76	22.80	48.65	38.37
7	7	39.89	55.88	49.25	31.78	53.47	50.02
8	8	52.23	64.72	68.66	48.18	70.91	52.19
9	9	56.81	88.32	72.32	54.68	72.04	57.01
10	10	59.66	94.05	75.57	60.22	74.97	65.53
11	11	74.81	97.19	80.35	68.74	.76.74	69.22
12	12	75.95	98.87	84.81	69.58	80.27	71.47

Table no 5: Dissolution Profile of F7, F8 & F9 formulations (1%, 1.5% & 2% of- PEG-6000)& Dissolution Profile of F10, F11 & F12 formulations (1%, 1.5% & 2%-Carbopol)

Serial no.	Time (min)	%release F 7	%release F 8	%release F 9	%release F 10	%release F 11	%release F12
1	1	3.66	2.60	2.24	3.98	3.25	5.39
2	2	7.43	5.86	3.66	6.38	5.18	14.19
3	3	24.58	16.31	14.66	7.79	30.16	16.03
4	4	36.80	35.39	28.08	18.72	33.26	20.73
5	5	40.17	37.00	35.65	22.45	36.56	28.55
6	6	44.31	39.08	41.06	35.45	46.12	31.86
7	7	47.81	42.90	43.18	46.62	52.13	36.00
8	8	61.47	57.89	52.99	48.05	68.66	53.67
9	9	73.12	68.18	67.01	68.71	71.31	60.79
10	10	74.73	70.07	73.56	76.62	78.79	67079
11	11	80.35	72.04	77.70	84.41	80.01	72.80%
12	12	84.77	74.29	80.11	88.35	86.78	76.74

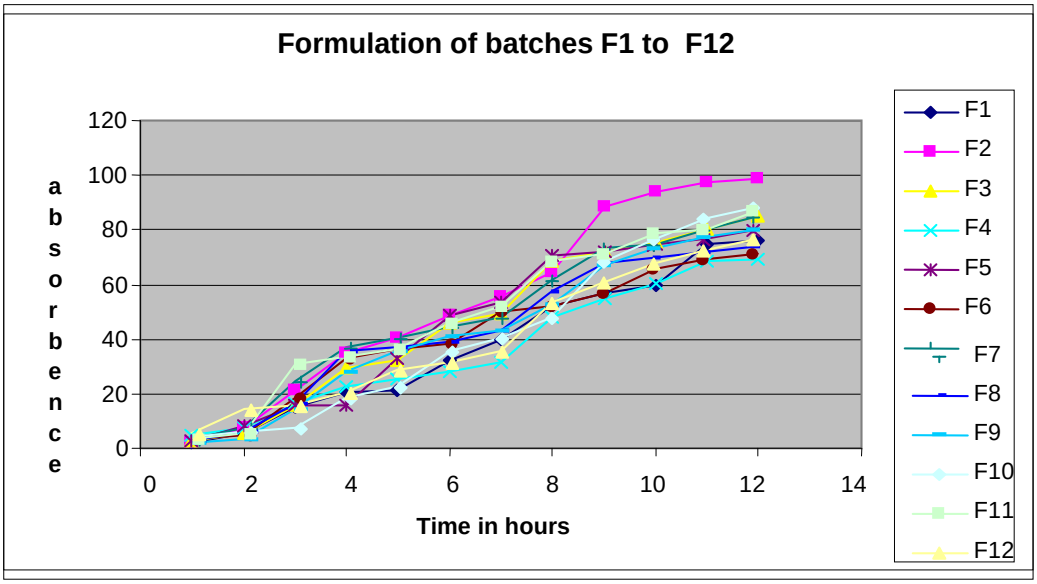

Figure no 1: In vitro release data of from F1 to F12 formulation (Comparative release profile of Guar gum, Tragacanth, Carbopol, and PEG-6000)

Swelling index:

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 upto 12 hours. Swelling index was calculated by using the following formula[9].

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

Where, Wt = *Weight of tablet at time t.*

W_0 = *Initial weight of tablet*

Table no 6: Swelling Index of Tablets of Batch F1 toF12

Batch	TIME (HRS)					
	0	1	2	3	4	5
F1	0	32.23	41.38	54.32	63.78	74.12
F2	0	49.25	61.54	72.90	82.37	92.54
F3	0	39.21	51.92	63.76	72.52	842
F4	0	29.09	39.45	51.32	61.12	71.97
F5	0	56.73	66.76	77.72	82.26	94.60
F6	0	45.65	53.35	64.32	75.45	80.09
F7	0	26.76	40.98	49.54	59.06	69.78
F8	0	35.45	45.78	59.87	69.58	81.02
F9	0	39.06	47.96	55.32	65.34	76.09
F10	0	25.87	36.54	47.86	57.98	69.96
F11	0	24.87	36.39	45.48	56.46	65.32
F12	0	22.46	34.97	42.56	54.23	60.85

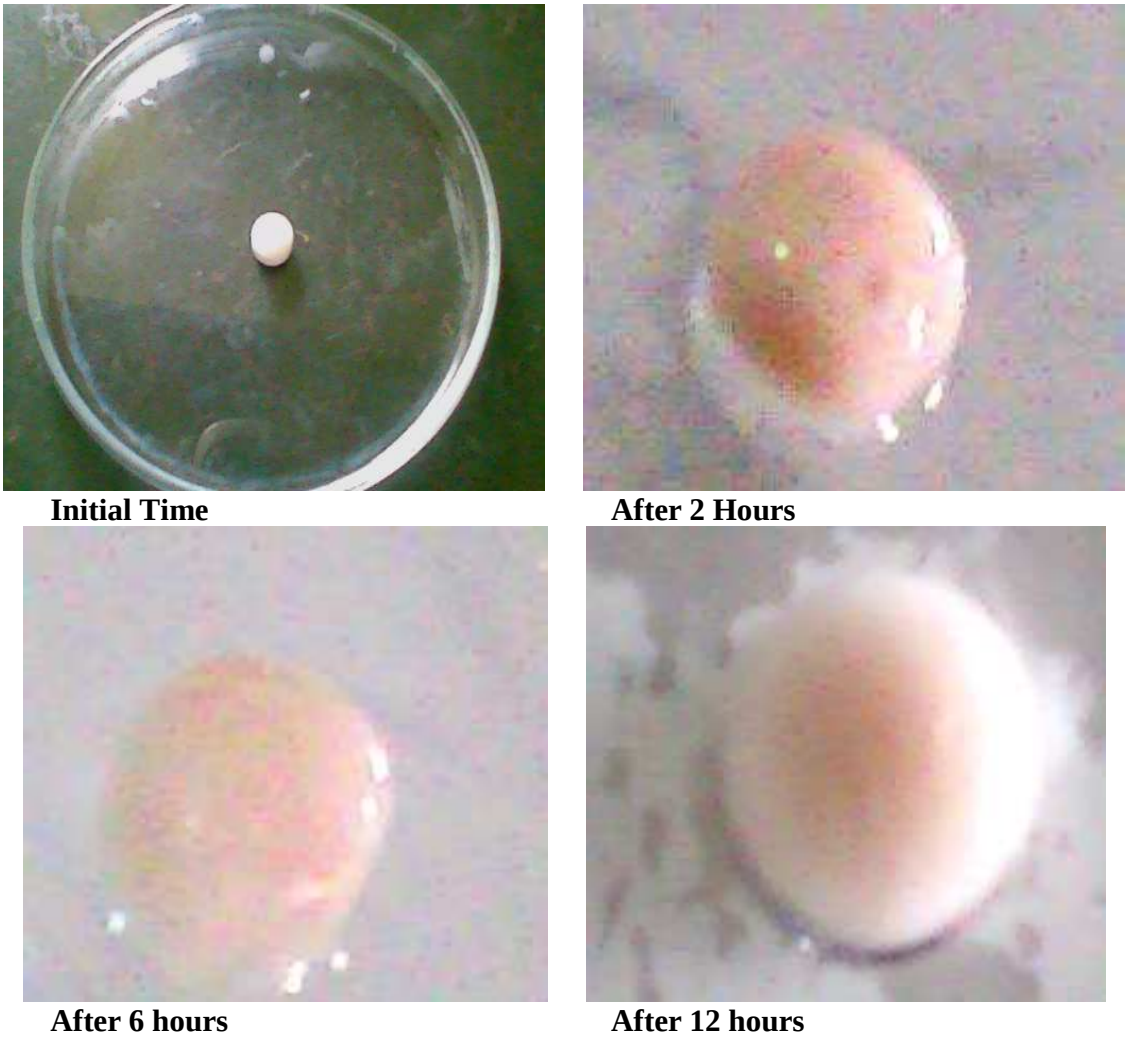

Figure no 2: Swelling studies of optimized formulation F2

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 results were shown in table no 7.

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.

Table no 7: Stability studies of optimized formulation (F2)

Tested after time (hrs.)	Cumulative% release(initial)	Cumulative% release(After 30 days)
1	2.16	2.19
2	7.63	7.88
3	21.41	21.39
4	34.67	35.48
5	40.17	41.11
6	48.85	48.01
7	55.85	56.35
8	64.72	64.23
9	88.32	86.11
10	94.05	93.32
11	97.19	97.45
12	98.87	98.16

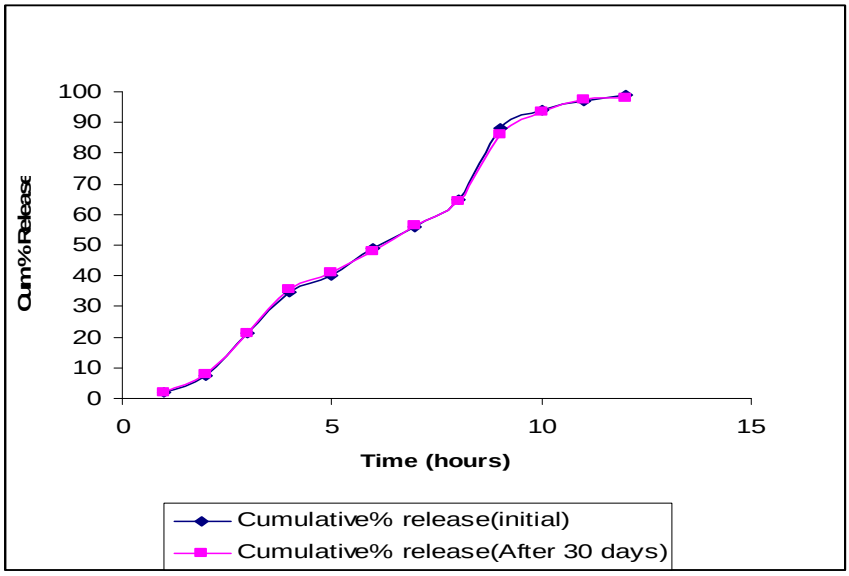

Figure no 3: Dissolution profile of Matrix Tablets of Isoniazid after one month Accelerated Stability studies.

RESULTS AND DISCUSSION

Oral route of drug administration is oldest and safest mode of drug administration. It posses several advantage. It provides accurate dosing without assistantship of administration. In conventional oral drug delivery system, there is little or no control over release of drug, and effective concentration at the target site can be achieved by administration of grossly excessive dosage form. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic

for an extended period of time. The design of proper dosage form is an important element to accomplish this goal.

Isoniazid is an antitubercular agent, with half life of 1.5-4 hours and requires multiple daily doses to maintain adequate plasma concentrations. So it is selected to prepare a sustained release tablet. The objective of this present study is to develop a sustained release tablet of Isoniazid which releases the drug in a sustained manner over a period of 12 hours, by using different polymers and study on polymer concentration effect on release pattern.

The present study was undertaken with an aim to formulate develop and evaluate Isoniaizd sustained release tablets using different polymers as release retarding agent. Preformulation study was done initially and results directed for the further course of formulation. Based on Preformulation studies different batches of Isoniazid were prepared using selected excipients. Granules were evaluated for tests Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. IR spectra studies revealed that the drug and polymers used were compatible.

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.

Stability study was conducted on tablets of Batch F2 stored at room temperature, 37^0 C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. After one month no significant changes were observed in any of the studied parameters during the study period, thus it could be concluded that formulation was stable. It was concluded that the tablets of batch F2 had considerable swelling behaviors and in vitro drug release. It was observed that tablets of batch F2 followed the Zero order release profiles.

Physicochemical evaluation of matrix tablet

The results of the Bulk Density, Tapped Density, Carrs Index, Hausners Ratio, Angle of Repose of granules and thickness, Hardness, weight variation, drug content, friability, and disintegration time of tablet are shown in Table 2 & 3.

In vitro Release Study

Table No.3 and 4 shows the data for in vitro release of Isoniazid from matrix tablet of batches F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, & F12 respectively. As follows the dissolution

profile shows the comparative release profile of Isoniazid with different concentration of different polymer from batches. The results were shown in table no 4 & 5.

CONCLUSION

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.

Stability study was conducted on tablets of Batch F2 stored at room temperature, 37^0 C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. After one month no significant changes were observed in any of the studied parameters during the study period, thus it could be concluded that formulation was stable. It was concluded that the tablets of batch F2 had considerable swelling behaviors and *in vitro* drug release.

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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