Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

DRUG RELEASE KINETIC STUDIES OF SUSTAINED RELEASE MATRIX TABLETS OF ISONIAZID

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ABSTRACT

Tablets are defined as solid dosage forms containing drug substance generally with suitable diluents and prepared by either compression or molding methods. Swellable matrices for oral administration are commonly manufactured as tablet by compression of hydrophilic micro particulate polymers. Therefore, the most appropriate classification for these systems is swellable matrix tablet. The 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.

KEYWORDS

Micro particulate polymers, Isoniazid, Swell able matrices and Sustained release.

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INTRODUCTON

The release of drug from swellable matrix tablet is based on glassy-rubbery. The transition of polymer results of water penetration into the matrix[1]. The interaction between water, polymer and drug are the primary factors for drug release. However, various formulation variables such as polymer grade, drug–polymer ratio, drug solubility and drug and polymer particle size, can influence drug release rate to greater or lesser degree[2]. The central element of the

mechanism of drug release in the gel layer, which is formed around the matrix[3-6]. The gel layer is capable of preventing matrix disintegration and further rapid water penetration. Water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion are phenomenon determining gel layer thickness[7-10]. Finally drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer[11].

EXPERIMENTAL METHODS

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 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 weight deviate from the average weight by more than the percentage shown in Table No.8 and none deviate by more than twice the percentage.

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[12].

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.

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[13].

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°C and the basket was set at 50 rpm. 10ml 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[14-20].

Swelling Index

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 upto 12 hours. Swelling index was calculated by using the following formula[21].

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

Where, Wt= Weight of tablet at time t, W_0 = Initial weight of tablet

Modeling of Dissolution Profiles

In vitro dissolution has been recognized as an important element in drug development under certain assessment of Bioequivalence. Several theories kinetics models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of 't' (time) related to the amount of drug dissolved form the pharmaceutical dosage system (Costa and Lobo, 2001). Whenever a new solid dosage form is developed or produced, the drug release/dissolution from solid pharmaceutical dosage form is necessary to ensure that the drug dissolution occurs in an appropriate manner. Several theories/ kinetic models describe drug dissolution form immediate and modified release dosage. These represents the drug dissolution profiles where f_t is a function of 't' (time) related to the amount of drug dissolved from the pharmaceutical dosage forms. The quantitative interpretation of the value obtained from the dissolution assay is facilitated by mathematical equation which translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms. In the present study, data of the *in vitro* release were fitted to different equations and kinetic models to explain the release kinetics of Isoniazid from the matrix tablets. The kinetic models used were a Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models[22-23].

RESULTS

Physicochemical Evaluation of Matrix Tablet

The results of the thickness, Hardness, weight variation, drug content, friability, disintegration time were as follows.

Drug content uniformity

The results of drug content of tablets are shown in Table No.5. The drug content of tablets were found to vary between 98.60%. To 102.06%, *Values are Mean ± SD (n=4).

***In vitro* Release Study**

Table No.6 to No.9 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, and F12 respectively. As follows the dissolution profiles shows the comparative release profile of Isoniazid with different concentration of different polymer from batches.

Table No.1: Chemicals used

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 No.2: Equipment used

S.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.

Thickness

Table No.3: Results of Thickness and Disintegration time

Parameter Batch	Thickness (mm)*	Disintegration Time(sec)*
F 1	4.4	196±
F 2	4.0	240
F 3	4.3	210
F 4	4.1	243
F 5	4.5	191
F 6	4.2	200
F 7	4.6	317
F 8	4.3	250
F 9	4.1	213
F 10	4.2	300
F 11	4.6	144
F 12	4.1	231

Mean weight variation

Table No.4: Result of weight variation, Hardness and Friability

Parameter Batch	Weight Variation (mg)	Hardness (Kg/cm2)*	Friability (%)
F 1	350.1	5.51	0.55
F 2	348.9	5.80	0.59
F 3	325.2	5.93	0.61
F 4	351.4	6.20	0.58
F 5	349.3	6.11	0.63
F 6	348.4	6.35	0.76
F 7	350.7	6.41	0.70
F 8	351.5	6.44	0.66
F 9	349.3	6.68	0.53
F 10	350.1	6.71	0.71
F 11	353.1	6.89	0.69
F 12	349.2	6.91	0.68

Table No.5: Result of Drug content uniformity

Parameter Batch	Drug Content (%)
F 1	99.50
F 2	98.60
F 3	100.02
F 4	99.59
F 5	99.38
F 6	99.05
F 7	99.60
F 8	102.06
F 9	100.62
F 10	99.50
F 11	100.02
F 12	101.01

Table No.6: Dissolution Profile of F1, F2 and F3 formulations (1%, 1.5% and 2% of guar gum)

Time (hrs)	%release F 1	%release F 2	%release F3
1	2.37	2.61	2.45
2	5.58	7.63	5.78
3	14.78	21.41	16.03
4	20.53	34.67	29.45
5	21.13	40.17	31.98
6	32.14	48.85	45.76
7	39.89	55.88	49.25
8	52.23	64.72	68.66
9	56.81	88.32	72.32
10	59.66	94.05	75.57
11	74.81	97.19	80.35
12	75.95	98.87	84.81

Table No.7: Dissolution Profile of F4, F5 and F6 formulations (1%, 1.5% and 2% of –tragacanth Gum)

Time (hrs)	%release F 4	%release F 5	%release F 6
1	4.66	2.65	3.37
2	7.80	8.30	4.98
3	16.15	15.95	18.64
4	22.86	16.03	32.62
5	22.55	32.66	36.68
6	22.80	48.65	38.37
7	31.78	53.47	50.02
8	48.18	70.91	52.19
9	54.68	72.04	57.01
10	60.22	74.97	65.53
11	68.74	.76.74	69.22
12	69.58	80.27	71.47

Table No.8: Dissolution Profile of F7, F8 and F9 formulations (1%, 1.5% and 2% of- PEG-6000)

Time (min)	%release F 7	%release F 8	%release F 9
1	3.66	2.60	2.24
2	7.43	5.86	3.66
3	24.58	16.31	14.66
4	36.80	35.39	28.08
5	40.17	37.00	35.65
6	44.31	39.08	41.06
7	47.81	42.90	43.18
8	61.47	57.89	52.99
9	73.12	68.18	67.01
10	74.73	70.07	73.56
11	80.35	72.04	77.70
12	84.77	74.29	80.11

Table No.9: Dissolution Profile of F10, F11 and F12 formulations (1%, 1.5% and 2%-Carbopol

Time (min)	%release F 10	%release F 11	%release F12
1	3.98	3.25	5.39
2	6.38	5.18	14.19
3	7.79	30.16	16.03
4	18.72	33.26	20.73
5	22.45	36.56	28.55
6	35.45	46.12	31.86
7	46.62	52.13	36.00
8	48.05	68.66	53.67
9	68.71	71.31	60.79
10	76.62	78.79	67079
11	84.41	80.01	72.80%
12	88.35	86.78	76.74

Table No.10: Comparison of all kinetic models

Batch code	Polymer concentration (%)	Zero order	First order	Higuchi	Korsmeyer-Peppas
F1	1% guar gum	0.9849	0.9342	0.8991	0.818
F2	1.5% guar gum	0.9801	0.8458	0.9506	0.7933
F3	2% guar gum	0.9761	0.9619	0.9011	0.8033
F4	1% Tragacanth Gum	0.9758	0.9415	0.8932	0.7962
F5	1.5% Tragacanth Gum	0.9489	0.9615	0.8665	0.7946
F6	2% Tragacanth Gum	0.9574	0.9864	0.9366	0.7978
F7	1% peg-6000	0.974	0.9618	0.9399	0.7855
F8	1.5% peg-6000	0.957	0.9652	0.9183	0.7803
F9	2% peg-6000	0.9825	0.017	0.9502	0.7824
F10	1% Carbopol	0.9716	0.871	0.9081	0.759
F11	1.5% Carbopol	0.9666	0.963	0.9111	0.0243
F12	2% Carbopol	0.9765	0.9364	0.8866	0.7864

Table No.11: 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

Table No.12: 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

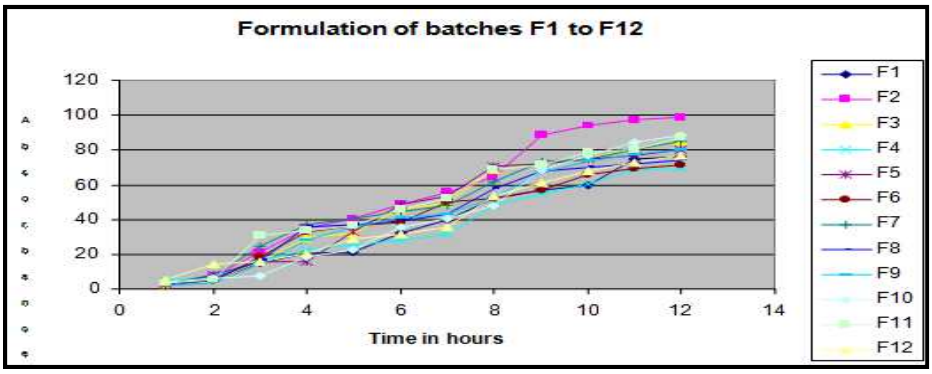


Figure No.1: *In vitro* release data of from F1 to F12 formulation (Comparative release profile of Guar gum, Tragacanth, Carbopol, and PEG-6000)

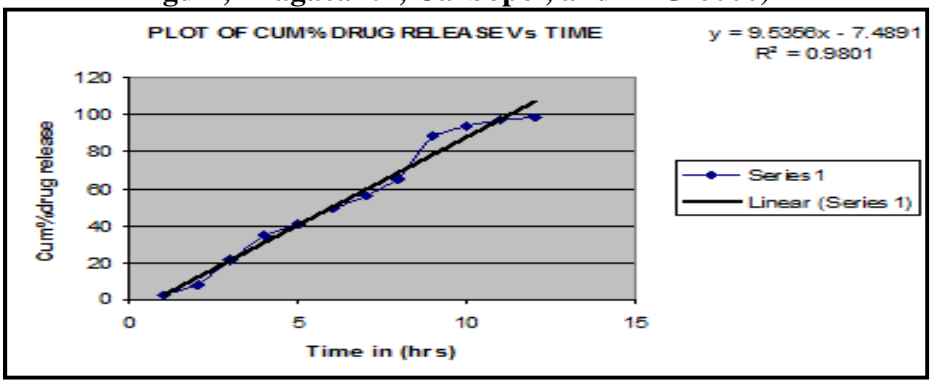


Figure No.2: Zero order release of optimized formulation (F2)

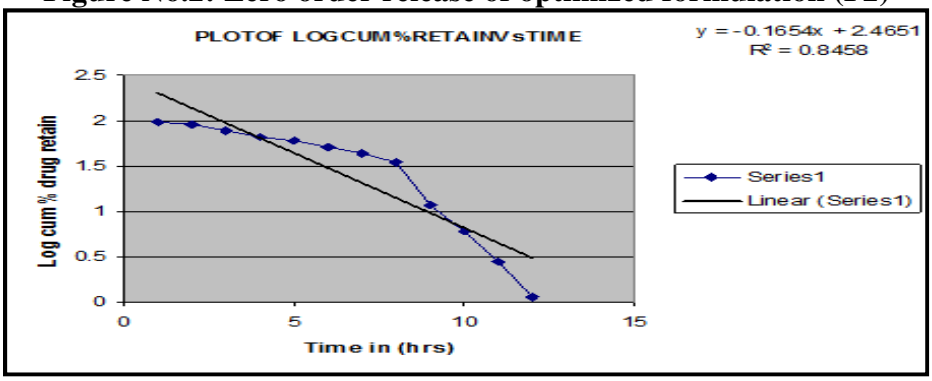


Figure No.3: First order release of optimized formulation (F2)

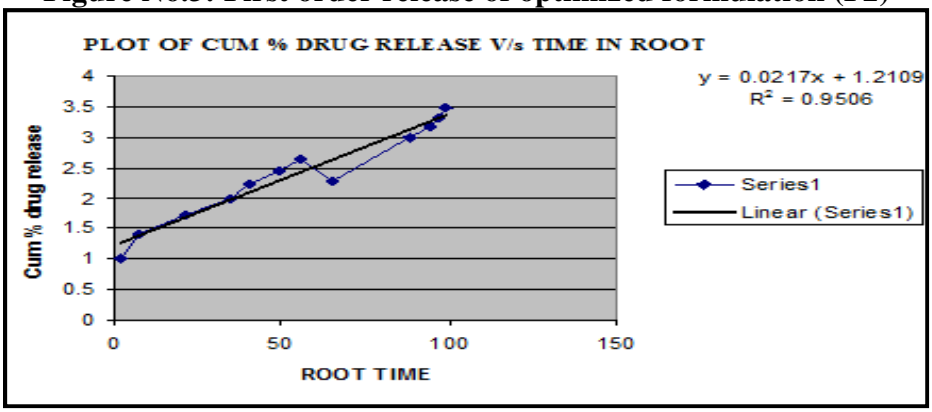


Figure No.4: Higuchi release of optimized formulation (F2)

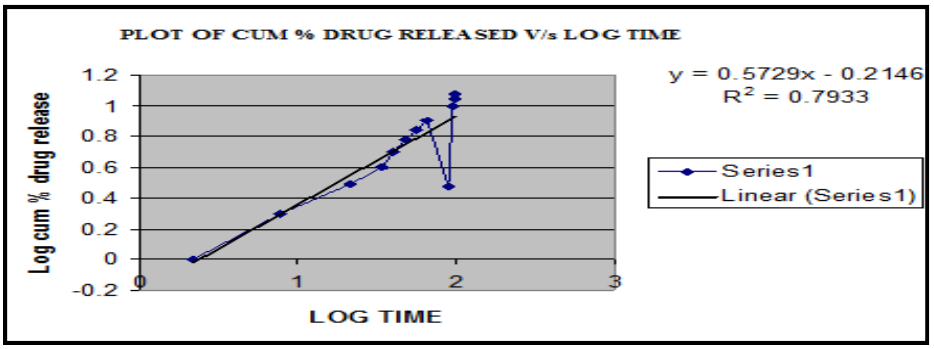
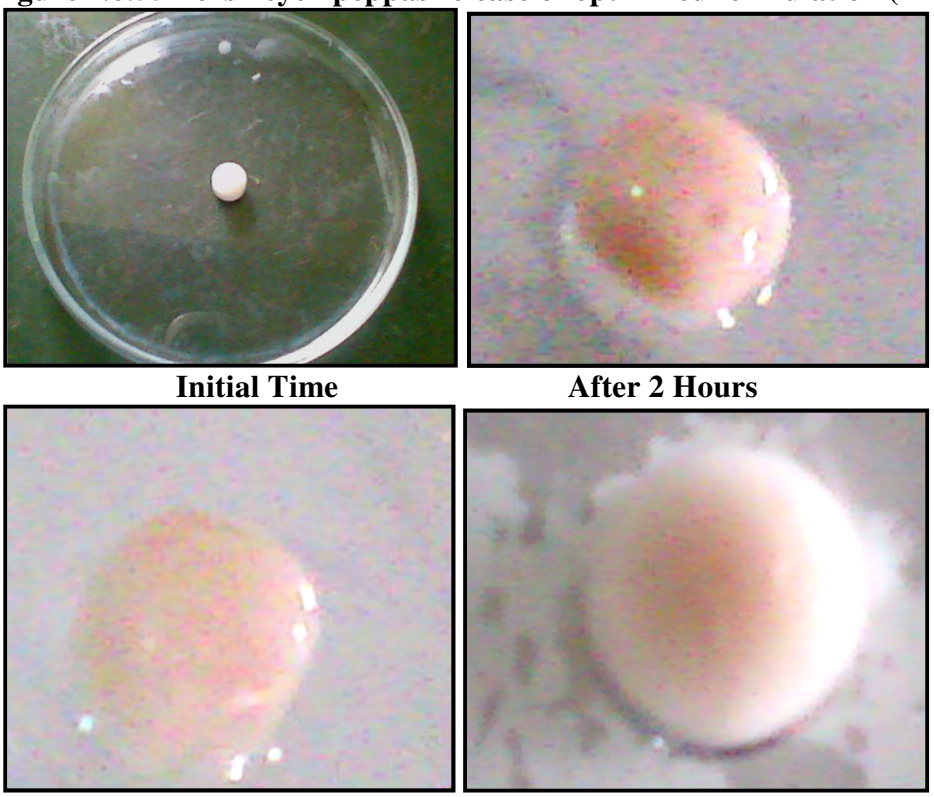


Figure No.5: Korsmeyer-peppas release of optimized formulation (F2)



Initial Time **After 2 Hours**

After 6 hours **After 12 hours**

Figure No.6: Swelling studies of optimized formulation F2

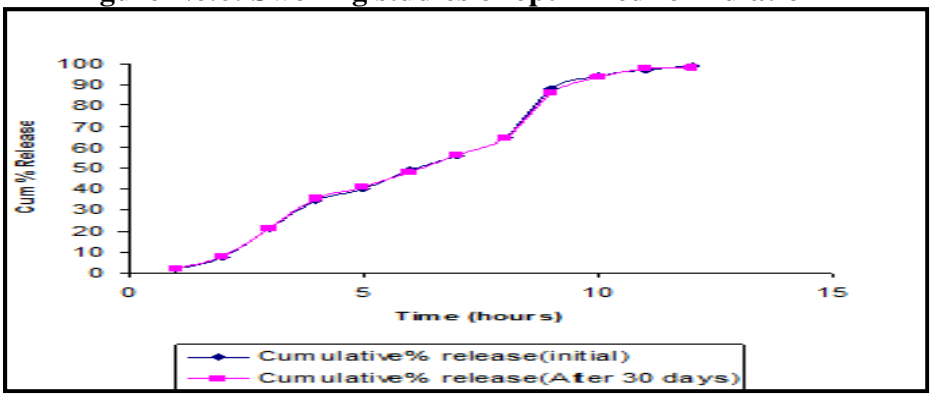


Figure No.7: Dissolution profile of Matrix Tablets of Isoniazid after one month Accelerated Stability studies

SUMMARY AND CONCLUSION

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, 37ºC 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.

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.

ACKNOWLEDGEMENT

The authors are sincerely thanks to the Department of Pharmaceutical Chemistry, Sri Adichunchanagiri University, Sri Adichunchanagiri College of Pharmacy, B.G. Nagara, Karnataka, India for providing the facilities to complete this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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