IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
August 2020 Vol.:19, Issue:1

Studies on Formulation and Evaluation of Sustained Release Matrix Tablets of Anti-Tubercular Drug Using Natural Polymer

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submission: 27 July 2020
Accepted: 02 August 2020
Published: 30 August 2020

www.ijppr.humanjournals.com

Keywords: Isoniazid, Sustained-release, Matrix tablet, Guar gum, Xanthan gum, Karaya gum

ABSTRACT

The objective of research work was to develop a drug delivery system (DDS) that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. The sustained release matrix tablets of Isoniazid were prepared by the wet granulation method using different natural polymers, such as guar gum, xanthenes gum and karaya gum. Then prepared tablets were evaluated for pre compressive parameters. Such as Bulk density, Tapped density, Compressible index, and Angle of repose, and then post-compression parameters were done for determination of Weight variation, Thickness& diameter, Hardness, Friability, Content uniformity. *In-vitro* dissolution studies results show Isoniazid sustained release formulation F1toF9 comprising of different grades of gum as guar gum, xanthan gum, and karaya gum showed drug release between 66.65% -96.78%. At the end of 10 hrs respectively and then *in-vitro* drug release kinetic study was done by zero-order, first order, Higuchi & Korsmeyer models. Then the Swelling index was calculated concerning time as 56.32%-92.55% at 8hrs. These systems continuously release the drug by dissolution-controlled and diffusion-controlled mechanisms.

INTRODUCTION:

Sustained Drug Delivery System[1-3]

Sustained Drug Delivery System is defined as designed to slowly release a drug in the body over an extended period. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. The drug delivery system is an interface between the patient and the drug. It may be a formulation of the drug to administer it for a therapeutic purpose or a device used to deliver the drug. This distinction between the drug and the device is important, as it is the criterion for regulatory control of the delivery system by the drug or medicine control agency. If a device is introduced into the human body for purposes other than drug administration, such as therapeutic effect by a physical modality or a drug may be incorporated into the device for preventing complications resulting from the device, it is regulated strictly as a device. There is a wide spectrum between drugs and devices, and the allocation to one or the other category is decided on a case by case basis. Sustained-release (SR) preparations are not new but several new modifications are being introduced. They are also referred to as “long-acting” or “delayed release” when compared to “rapid” or “conventional” release preparations. The term sometimes overlaps with “controlled release which implies more sophisticated control of release and not just confined to the time dimension.

MATERIALS AND METHODS:

MATERIALS:

Isoniazid is a Purchased sample from Loba Chemie Pvt. Ltd. Mumbai, India. Guar gum, Xanthan gum, Gum karaya & Lactose, Disodium hydrogen phosphate, Potassium dihydrogen phosphate is obtained from Sun Chem Pvt. Ltd. India. Talc, HPMC K4M, Magnesium stearate & HCl is obtained from Loba Chemie Pvt. Ltd. Mumbai, India.

METHODS:

Preparation of Isoniazid Matrix Tablets[4]

Sustained release matrix tablets of Isoniazids were prepared by wet granulation method using different natural polymers such as guar gum, xanthan gum, and karaya gum respectively. The composition of various Isoniazid sustained-release tablets is given in Table 1. Isoniazid, polysaccharide, lactose, and HPMC K4M were mixed in a polybag, and the mixture was passed through a mesh (No. 40). Granulation was done using a starch paste. The wet mass was passed through mesh No 16. Thereafter, the granules were then dried at 50ºC for about 2 h with the residual moisture content of 2 to 3% w/w. The dried granules were lubricated with magnesium stearate and talc for 2 min. Tablets were compressed using a Rotary tablet machine with 8 mm standard concave punch.

Table No. 1: Tablet composition of different formulations of Isoniazid sustained release matrix tablets

Ingredients (Mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Isoniazid	150	150	150	150	150	150	150	150	150
Gum Karaya	20	40	60	-	-	-	-	-	-
Guar gum	-	-	-	20	40	60	-	-	-
Xanthan gum	-	-	-	-	-	-	20	40	60
Lactose	116	96	76	116	96	76	116	96	76
HPMC K4M	10	10	10	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	1	1	1	1	1	1	1	1	1

Evaluation of pre-compressive parameter[5-9]

Bulk density

This term refers to a measure used to describe the packing of particles of granules. Bulk density pb is defined as the ratio of the mass of powder to the bulk volume and is expressed as g/cm^3. The Bulk density was determined by the following formula.

$$pb = M / Vp$$

Where, **pb** = Bulk Density **M** =Weight of Blend take **Vp=**Final volume of blend in cm^3 The results of bulk density of prepared formulation as given in table 2.

Tapped density (Dt): It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend, on the mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. 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.

The results of the tapped density of prepared formulation as given in table 2.

Compressibility Index

The compressibility Index measures the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. There are frequently greater interparticle interactions and a greater difference between bulk and tapped densities was observed. The compressibility index was calculated using the following equation.

$$\text{Compressibility index} = [(Dt-Db)/Dt] \times 100$$

Where, **Dt** = tapped density, **Db** = bulk density

The results of the compressibility index of prepared formulation as given in table 2.

Angle of repose

The angle of repose of powder drug was determined by the fixed funnel and cone method. A petri dish was taken and its diameter was determined. A funnel was fixed above the petri dish and 4 g of Isoniazid was poured from the funnel with its tip at 2 cm height 'H' until the apex of the heap formed reached the lower end of the funnel. The mean diameter, 2R, of the base for the powder cone was measured and the angle of repose was calculated by

$$\tan\Theta = H/R$$

Where H is the height of the cone R is the radius of the cone base.

The results of the angle of repose of prepared formulation as given in table 2.

Evaluation of Post compression Parameters[10-20]

Weight variation

To study weight variation twenty tablets of the formulation were weighed using an Essae electronic balance and the test was performed according to the official method. Exact 20 tablets were randomly selected from each batch and weighed individually weighed for checking of weight variation. The results of the weight variation of prepared formulation as given in table 3.

Thickness and diameter

The thickness of the tablets was determined using a slide caliper scale. Five tablets from each batch were used, and average values were calculated. Tablet thickness should be controlled within 5% variation of standard value. The results of the thickness and diameter of the prepared formulation as given in table 3.

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in the manufacture, packaging, and shipping. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. The results of the hardness of prepared formulation as given in table 3.

Friability

Friability of the tablets was determined by 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. Pre weighed 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.

$$F = (1-W0/W)\ 100$$

Where W0 is the weight of the tablets before and W is the weight of the tablets after the test. The results of the friability of prepared formulation as given in table 3.

Content uniformity

Ten tablets from each formulation were taken, crushed and mixed. The mixture of the equivalent mixture was extracted thoroughly with 100 ml of pH 6.8 phosphate buffer. The amount of Isoniazid present in each sample was determined using a UV spectrophotometer at 263 nm. The results of the content uniformity of prepared formulation as given in table 3.

***In-vitro* dissolution studies**

The *in-vitro* dissolution study was conducted as per the United States Pharmacopoeia (USP) XXIV. The rotating paddle method was used to study the drug release from the tablets. The dissolution medium consisted of 900 ml of 0.1N HCl and phosphate buffer (pH 6.8). The release was performed at 37°C ± 0.5°C, at a rotation of speed of 50 rpm, a 5 ml sample solution was withdrawn at a specified interval of time and the volume was replaced with a fresh medium. The solution sample was filtered through Whatman filter paper No.40 and analyzed for Isoniazid. The absorbance of the withdrawn sample was measured at λ max 263 nm using a UV visible Spectrophotometer. The cumulative percentage of drug release was calculated using the equation obtained from a standard curve of the drug in 0.1N HCl and phosphate buffer pH 6.8. The immediate-release part for sustained release Isoniazid was also calculated. The results of *in-vitro* dissolution studies of prepared formulation as given in table 4.

***In-vitro* drug release kinetic study of tablets**

In short, the results obtained from in vitro release studies were plotted in four kinetics models of the data treatment as follows:

- Cumulative percentage of drug release Vs. Time (zero-order rate kinetics)
- Log the cumulative percentage of drug retained Vs. Time (first-order rate kinetics)
- Cumulative percentage of drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

The results of the *in-vitro* drug release kinetic study of tablets of prepared formulation as given in table 5.

Swelling index

Six Matrix tablets were individually weighed (W1) and placed separately in Petri dishes with 5 ml of phosphate buffer of pH 6.8. At the time interval of 1, 2, 4, 6, and 8 h, the tablet was removed from the Petri dish and excess water was removed carefully using the filter paper. The swollen tablet was then reweighed (W2) and the percentage hydration was calculated using the following formula.

$$SI\ (\%) = \frac{(\text{Weight of Swollen Tablet} - \text{Initial Weight of Tablet})}{(\text{Initial Weight of Tablet})} \times 100$$

RESULT AND DISCUSSION:

Drug-excipients compatibility study

The Isoniazid identified by IR Spectrum, which shows the characteristics absorption peak of various functional groups. The Isoniazid –C-H peak at 3000 cm^{-1}, -OH at 3500 cm^{-1}, -NH at 3300 cm^{-1}, cm^{-1}, C=O at 1630 cm^{-1}, and –C-N at 1500 cm^{-1}.Characteristics peak of isoniazid was present in FTIR spectra of all binary mixture, thus any change in their positions not found and also no chemical interaction between the drug and excipient observed. The results of the FTIR of prepared formulation as given in graph 2.

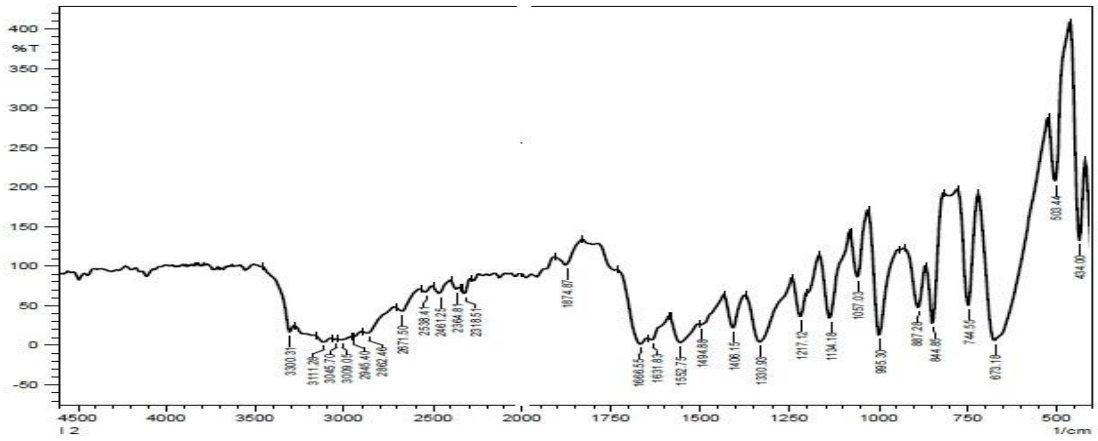


Figure No. 1: FTIR spectra of Isoniazid

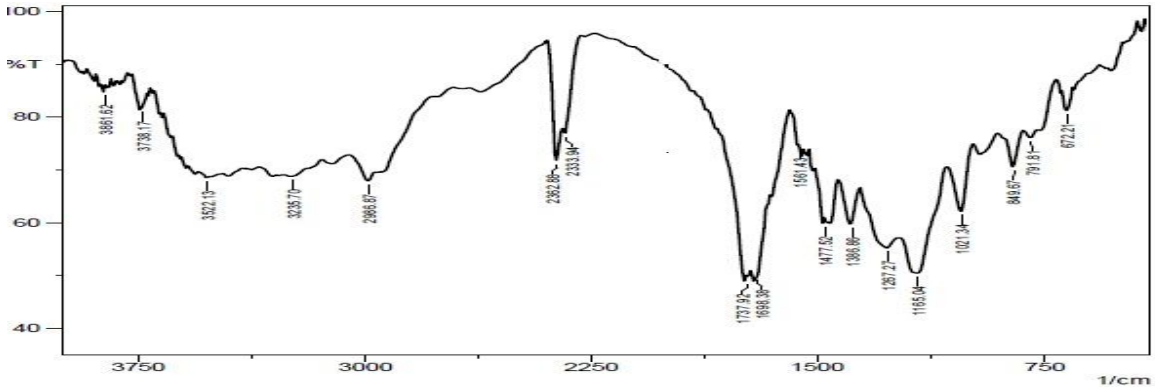


Figure No. 2: FTIR spectra of Isoniazid formulation

Evaluation of pre-compressive parameters

The bulk density of isoniazid was found in the range 0.51 to 0.58 (gm\ml) for formulation F1-F3 0.59 to 0.52 (gm\ml) for F4-F6 and 0.52 to 0.53 (gm\ml) for F7-F9. The tapped density of isoniazid was found in the range 0.86 to 0.68 (gm\ml) for formulation F1-F3, 0.62 to 0.63 (gm\ml) for F4-F6 and 0.64 to 0.66 (gm\ml) for F7-F9. It was further supported by high compressibility index value 16.34 to 16.39 % for formulation F1-F3, 16.93 to 17.93 % for F4-F6, and 17.50 to 15.58 % for F7-F9. The drug is mixed with flow promoters like diluents and lubricants to increase flow property. All the formulations F1 to F9 exhibited the angle of repose value between 25.33 to 30.11%. (Table 2)

Table No. 2: Physicochemical evaluation of various Isoniazid sustained release formulations

Formulation code	Bulk density	Tapped density(TBD) (g/ml)	Compressibility index (%)	Angle of repose
F1	0.51	0.86	16.34	25.71
F2	0.53	0.63	15.43	26.40
F3	0.58	0.68	16.39	26.12
F4	0.59	0.62	16.93	27.79
F5	0.54	0.63	14.55	26.58
F6	0.52	0.63	17.93	30.11
F7	0.52	0.64	17.50	25.85
F8	0.54	0.67	19.19	26.55
F9	0.53	0.66	15.58	26.72

Evaluation of post-compressive parameters

The prepared tablets were evaluated for their various physicochemical properties. The tablets were white, circular and were found to be uniform concerning weight variation (300.12 to 301.02 mg), thickness (5.13 to 5.11 mm), hardness (5.54 to 5.31kg/cm2) and friability (0.2 to 0.27 %) and content uniformity (97.99 to 98.16 %). All of the different batch F1 to F9 of tablets were found within acceptable limits. (Table 3)

Table No. 3: Physicochemical evaluation of various Isoniazid sustained release formulations

Formulation Code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Content uniformity (%)
F1	300.12	5.13	5.54	0.2	97.99
F2	299.14	5.15	5.25	0.3	98.52
F3	299.36	5.11	5.12	0.3	98.17
F4	301.34	5.09	5.23	0.1	97.85
F5	302.35	5.04	5.18	0.24	98.42
F6	300.01	5.13	5.27	0.4	99.02
F7	299.84	5.12	5.14	0.12	98.92
F8	302.23	5.09	5.26	0.20	97.73
F9	301.02	5.11	5.31	0.27	98.16

***In-vitro* dissolution studies**

Isoniazid sustained-release formulations F1- F9 comprising of different grades of gum as guar, xanthan, and karaya, showed drug release between 66.65- 96.78 % at the end of 10 hrs respectively. The results of the *in-vitro* drug release of sustain release matrix tablets are given in the below graph.

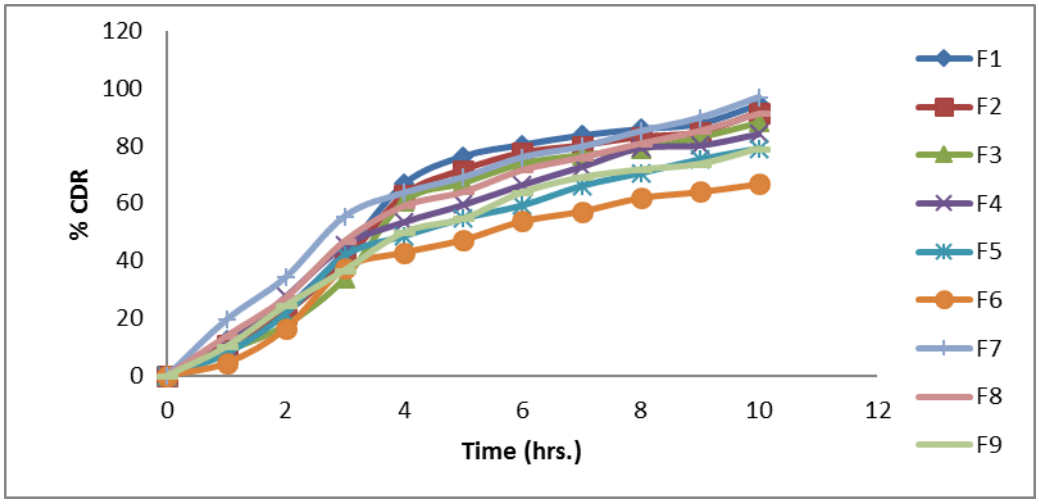


Figure No. 3: *In-vitro* dissolution profile of Isoniazid sustained-release formulations F1-F9

***In-vitro* drug release kinetic studies**

In-vitro drug release data were fitted in different models such as zero-order, first-order, and Higuchi models to evaluate drug release kinetic and also fitted in the Korsmeyer peppas model to evaluate the mechanism of drug release(Table 4). Isoniazid sustained-release tablet showed a first-order drug release, except tablet containing Xanthan gum which followed Higuchi kinetic. For all sustained-release tablets n value of power, the law is > 1indicated super case II transport, diffusion with swallowing.

Table No. 4: *In-vitro* drug release kinetic studies of Isoniazid sustained-release tablets

Formulation code	Zero-order	First-order	Higuchi	Korsemyer pepas	n-value
F1	0.8566	0.9648	0.9308	0.9839	1.210
F2	0.8709	0.9710	0.9408	0.9903	1.279
F3	0.8760	0.9728	0.9398	0.9771	1.390
F4	0.9185	0.9930	0.9781	0.9685	1.11
F5	0.9234	0.9911	0.9782	0.9685	1.256
F6	0.8875	0.9616	0.9571	0.9532	1.539
F7	0.9213	0.9112	0.9761	0.9887	1.088
F8	0.9240	0.9285	0.9787	0.9948	1.076
F9	0.9268	0.9884	0.9812	0.9872	1.073

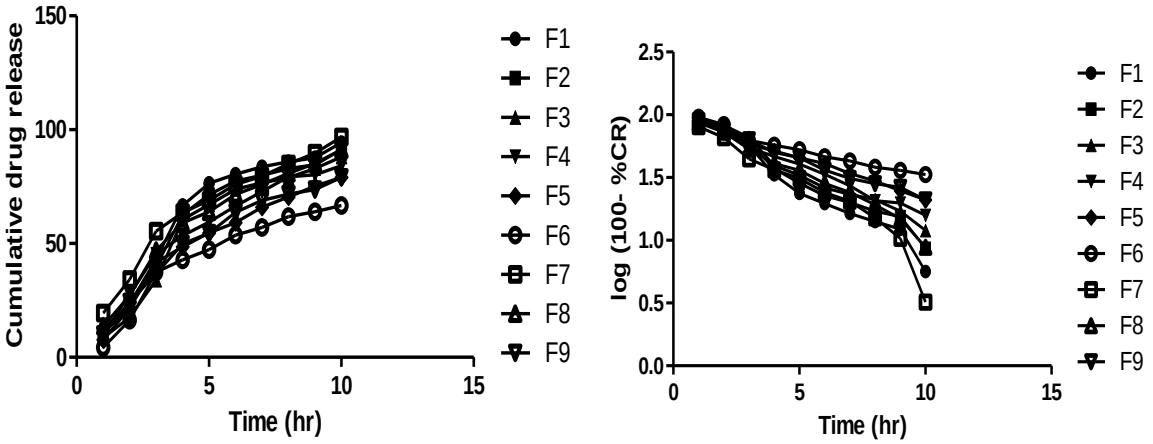


Figure No. 4: Zero-order & first-order drug release kinetic studies of Isoniazid sustained-release formulations F1- F9

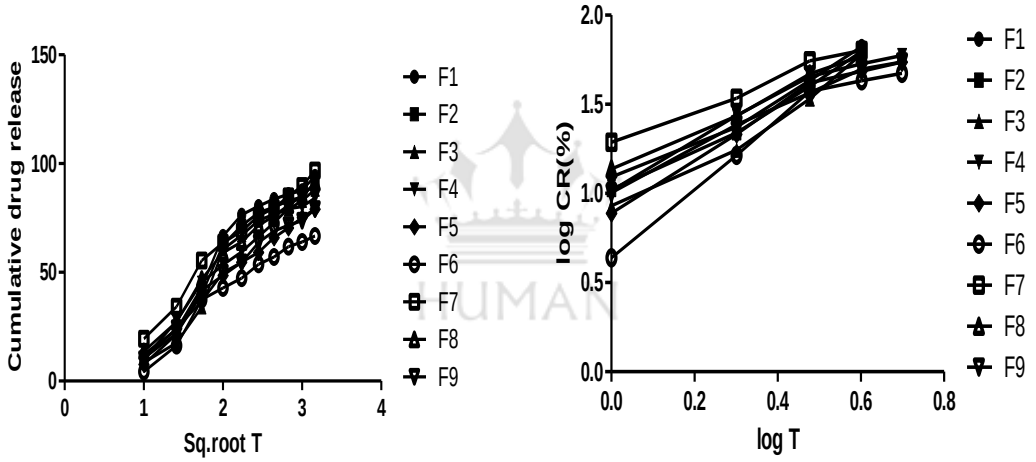
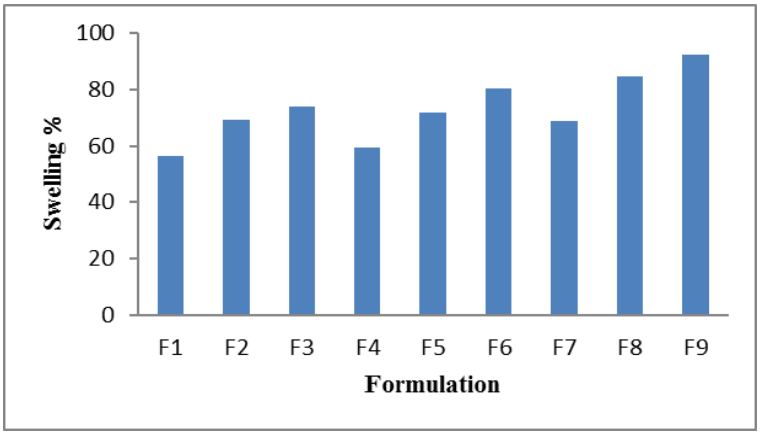


Figure No. 5: Higuchi model & Korsmeyer peppas kinetic studies of Isoniazid sustained-release formulations F1- F9

Swelling index-The swelling index was calculated concerning time as 56.32 to 92.55 % at 8h.



. **Figure No. 6: Swelling studies of Isoniazid sustained-release formulations F1- F9**

CONCLUSION:

The sustained release matrix tablet of Isoniazid was successfully formulated and evaluated. In the present study, it was found that the Isoniazid F3 formulation exhibited satisfactory results. The study demonstrated that the formulated tablet of Isoniazid F3 is capable of treating chronic disease conditions like tuberculosis and is also free of gastric side effects. From results obtained, it was concluded that the formulation of sustain release matrix tablet of Isoniazid containing gum Karaya, guar gum, xanthin, and HPMC as polymer was taken as an ideal or optimized formulation for 12 hrs release as it fulfills all the requirement of the sustained-release dosage form. It was concluded from current results that either replacement one of this polymer such as guar gum,karaya gum and xanthan gum by other natural polymer or sustained release matrix tablet prepared by another method, may result in the introduction of better formulation of sustained release matrix tablet of Isoniazid with more antitubercular activity.

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