Formulation and *in vitro* evaluation of sustained release matrix tablets using cross-linked natural gum

Qurrat Ul Ain Jamil*[1,4], Muhammad Irfan Masood[1], Muhammad Nauman Jamil[2], Imran Masood[3] and Shahid Muhammad Iqbal[4]

[1]Institute of Pharmaceutical Sciences, University of Veterinary and Animal Sciences, Lahore, Pakistan
[2]Faculty of Pharmacy, University of Sargodha, Sargodha, Pakistan
[3]Faculty of Pharmacy and Alternative Medicine, Islamia University of Bahawalpur, Bahawalpur, Pakistan
[4]Drugs Regulatory Authority of Pakistan, Islamabad, Pakistan

Abstract: Polysaccharide gums because of their biocompatibility, biodegradability and non-immunogenic properties are considered as the best choice for preparing sustained release tablets as compared to their synthetic counterpart. The cross linking of natural gums in matrix tablets increase the sustained release property of matrix tablets. Isoniazid is a first line therapy of tuberculosis, belongs to BCS I with half-life of 3-4 hours. These characteristics make isoniazid a good candidate for sustained release dosage form. Karaya gum crossed linked with trisodium tri metaphosphate was used as release rate retardant for preparing isoniazid cross-linked matrix tablet. Total 8 sustained release formulations were prepared. Both granules and tablets were evaluated under *in vitro* condition against different parameters. Dissolution studies were performed with all eight formulations for 12 hours using USP apparatus I. Four formulations designated as F1, F2, F3, F4 have drug and karaya gum while other four formulations F5, F6, F7, F8 have drug and crossed linked polymer in ratios of 1:1, 1:2, 1:3 and 1:4 respectively. Dissolution data was analyzed by using different kinetic models. Best fit model for most efficient formulation was zero order while release mechanism was super case I. Formulation 8 showed sufficiently slow release kinetics and about 83% of drug was released in 10 hours, indicating that cross-linked karaya gum proved efficient in preparing sustained release tablets.

Keywords: Sustained release tablet, isoniazid, dissolution release profile, release models, swelling index.

INTRODUCTION

Sustained release formulations are majorly favored and gaining importance because of their high patient compliance both in acute and chronic diseases. They show prolonged therapeutic action with continuous release of drug over an extended period of time. Sustained release formulation as matrix tablets from hydrophilic polymer are popular due to low cost, less toxicity and minimum incidence of dose dumping for hydrophilic and hydrophobic drugs (Hiremath and Saha, 2008; Varshosaz *et al.*, 2006). Among hydrophilic polymers, natural polymers such as polysaccharide gums have more advantage over their synthetic counterparts because of their natural abundance, biocompatibility, biodegrade-ability and non-immunogenic nature (Bhardwaj *et al.*, 2000; Coviello *et al.*, 2007). Use of a cross linking agent in natural gums has been reported to increase sustained release profile of many drugs (Varshosaz *et al.*, 2006).

Tuberculosis (TB) is a contagious chronic bacterial infection and is one of the leading causes of death worldwide with millions of people being infected every year (WHO, 2016b). It is one of the biggest health problems in Pakistan with 0.42 million patients diagnosed every year (WHO, 2015). Patients are noncompliant due to multiple drugs and dosing regimen per day (Burman *et al.*, 1997). Isoniazid is the first line therapy for tuberculosis available in different conventional dosage forms. It belongs to BCS I class with half-life of 3-4 hours, given orally. These characteristics make isoniazid a suitable candidate for oral sustained release formulation. So, cross-linked karaya gum based sustained release matrix tablets of isoniazid were prepared and characterized by its *in vitro* dissolution profile.

MATERIALS AND METHOD

Materials

Isoniazid, magnesium stearate, sodium hydroxide, lactose and starch were donated by Schazoo Zaka Ltd. Pakistan. Karaya gum and trisodium trimetaphosphate was purchased from Sigma-Aldrich, USA. All chemicals and solvents were of analytical grade and used without further purification. Water used in the experiments was double distilled.

Preparation of sustained-release tablets

Karaya gum was cross linked with trisodium trimetaphosphate as described previously (Reddy *et al.*, 2012). Briefly, 1g of trisodium trimetaphosphate was dissolved in 50ml of water and mixed with 5ml of NaOH (0.1N). In another beaker 1g of karaya gum was mixed thoroughly in 50ml water. Both solutions were mixed

*Corresponding author: e-mail: sarakhan6130@yahoo.com

together slowly with continuous stirring for 2 hours. After mixing, 20 ml of the final solution was poured in 5 petri dishes each and kept in hot oven at 60ºC for 24 hours. The dried material was crushed and passed to sieve of 200µ. This modified gum was used in formulation. Four formulations were prepared by using drug and karaya gum in ratio of 1:1, 1:2, 1:3, and 1:4 respectively and designated as F1, F2, F3, F4. The other four formulations designated as F5, F6, F7, F8 contained drug and cross-linked polymer in ratio of 1:1, 1:2, 1:3 and 1:4 respectively. Tablets were prepared by wet granulation and each tablet contained 150mg of isoniazid. Detailed formulation of each of tablet is described in table 1.

Evaluation of sustained release granules of isoniazid

a) Angle of repose

Angle of repose was determined by using the funnel method. Funnel was adjusted in such a way that its tip was in contact to the peak of granules heap. After making described adjustment, pre-weighed granules were allowed to flow through it and cone of the granules was obtained. The diameter and height of the granules cone was measured. Angle of repose was then calculated by using the following equation. $\tan \theta = h/r$

Where, "h" and "r" are the height and radius of the granules cone respectively. The value of the angle of repose less than 35 is considered good (Mehsud *et al.*, 2016).

(b) Bulk density

Loose bulk density (LBD) and tapped bulk density (TBD) were determined according to method described previously. (Elkhodairy *et al.*, 2014) Briefly, granules (5g) from each formulation were poured into 10ml measuring cylinder. The initial volume of the granules from each formulation was measured. After that, all the cylinders were allowed to free fall from the height of 2.5cm onto a hard surface at the intervals of 2 seconds. Final volume was measured when no further change in the volume was noted. Both LBD and TBD were calculated by using following formulas.

Loose bulk density = weight of the powder/initial volume of the packing

Tapped bulk density = weight of the powder/tapped volume of the packing.

(c) Compressibility index

Compressibility index of granules was calculated by using formula of Carr's compressibility index.

Carr's index (%) = [(TBD – LBD) × 100]/TBD

The value of compressibility index less than 15 is considered good (Reddy *et al.*, 2003).

(d) Total porosity

Total porosity was calculated from initial volume and tapped volume of the same granules by using the following formula.

Total porosity = initial volume – tapped volume/initial volume × 100

Total porosity less than 48% is considered good. (Bose *et al.*, 2013; Reddy *et al.*, 2003)

(e) Hausner's ratio

Hausner's ratio was determined by dividing tapped density with initial density of granules. The value of Hausner's ratio less than 1.18 is considered good (Elkhodairy *et al.*, 2014).

(f) Drug contents

Granules were powdered and volume equivalent to 100mg of isoniazid was mixed in 200ml of distilled water with continuous stirring to dissolve the isoniazid. After allowing adequate time for mixing, distilled water was added to make the final volume of 500ml and filtered. After filteration solution was diluted with distilled water to the concentration of 5µg/ml and absorbance was measured at 263nm. Percentage of drug was calculated by taking value of E1% as 307 (Gohel and Sarvaiya, 2007; Hiremath and Saha, 2008).

Evaluation of sustained-release matrix tablets of isoniazid

(a) Weight variation:

Weight variation of tablets was determined by weighing 20 tablets on the pre calibrated weighing balance. (Mehmood *et al.*, 2016) Percentage variation from standard weight was calculated by following formula.

Weight variation = [(weight of tablet - standard weight of tablet)/standard weight of tablet] ×100

Standard weight of the tablet was 750mg and the criterion for uniformity of weight of uncoated tablets for more than 250mg weight tablet was taken as

Permitted deviation (%) for ≥ 18 of 20 tablets ±5

Permitted deviation (%) for ≤ 2 of 20 tablets ±10

(b) Variation of thickness and diameter

Thickness and diameter of 10 tablets were measured with the help of Vernier Caliper.(Reddy *et al.*, 2003) The percentage variation of thickness and diameter was determined by using following formula.

Variation of thickness = [(thickness of tablet - standard thickness of tablet)/standard thickness of tablet]×100

(c) Hardness

Hardness of tablet was checked by using Ewreka hardness tester. The breaking force was applied on the tablet by a beam that was fastened to the end of pivot. The value was determined that just broken the tablet. Six tablets from each formulation were tested. The criterion of acceptance of hardness is between 4-11 Kg/cm^2 (Mehmood *et al.*, 2016).

(d) Friability

Friability of tablets was checked by using Roche fribilator. (Emami *et al.*, 2010) Twenty tablets from each

formulation were weighed and placed in Roche fribilator. These tablets were tested for 4 minutes at 25 rpm. Tablets were fallen from height of 6 inches. The tablets were again weighed and percentage of weight loss was determined. The test was performed in triplicate. Percentage of loss of weight should not be more than 1%. Weight loss was determined by the given formula.

%age weight loss= (difference in weight of tablets/initial weight of tablets) ×100

(e) Drug content

Twenty tablets were powered and volume equivalent to 100mg of isoniazid was taken in 500ml of volumetric flask. Distilled water about 200ml was added and stirred well to dissolve the isoniazid. Then volume was raised to 500ml with distilled water. Mixture was filtered and diluted with distilled water to 5µg/ml and absorbance was measured at 263nm. Percentage of drug was calculated by taking value of E1% as 307 (Gohel and Sarvaiya, 2007; Hiremath and Saha, 2008).

(f) Swelling and erosion behavior

Swelling and erosion behavior of sustained-release matrix tablets of isoniazid was determined by calculating swelling index (Moin and Shivakumar, 2010). From each formulation 3 tablets were weighed separately and then dipped into distilled water. After every hour tablets were weighed by taking tablets out of the distilled water and removing excess water by filter paper. The swelling index was determined by the given formula.

Swelling index= (Difference of weight at time (t) with initial weight/initial weight) ×100

(g) In vitro release

USP apparatus type I was used to determine *in vitro* release of sustained-release matrix tablets of all formulations by previously described method with little modifications.(Hiremath and Saha, 2008) Standard curve was constructed from known concentrations of drug. 900ml of distilled water was added in each vessel and temperature was maintained between 35-39°C. The revolutions were set 50 rpm and the study was conducted for 12 hours. First sample of 5 ml was collected at interval of 2 hours followed by sampling after every hour. The volume taken was replaced with equal volume of distilled water. Samples were filtered, properly diluted and analyzed at wavelength of 263nm.

Application of release models on dissolution profile

(a) Zero order model

Zero order model is also called the concentration independent model. It is the model that governs when dosage form of drug does not disintegrate and release of drug occurs slowly with passage of time. The release of drug per unit time remains same for the whole time. The equation that governs zero order model is

$M=M_0-K_0t$

$K_0= (M_0-M)/t$

Where "M" is amount of drug at time "t" and "M_0" is amount of drug at time zero. "K_0" is the zero order constant. The graph was drawn between cumulative drug release verses time to show this model (Costa and Sousa Lobo, 2001).

(b) First order model

First order model that is also concentration dependent model describes the absorption and elimination of some drugs. The model governs such dosage form in which solid particle of drug dissolute into the medium from the surface. The equation governs this model is mentioned

$\ln M = \ln M_0 K_1 t$

$(\ln M - \ln M_0)/t = K_1$

Where, "K_1" is the first order constant, "M" is the amount of drug at time "t" and "M_0" is amount of drug at time zero. So, the graph of this model was drawn ln of cumulative concentration released verses time (Costa and Sousa Lobo, 2001).

(c) Higuchi model

Higuchi model is used to determine the trend of release of water soluble and less water soluble drugs from matrix system. The matrix tablet can be solid and semi solid. The equation governs this model is

$Q_t = kHt^{1/2}$

Where "Q_t" is the amount of drug dissolved at time "t" and "kH" is release constant. The graph to represent the Higuchi model was between cumulative drug release verses square root of time (Costa and Sousa Lobo, 2001).

(d) Hixson crowell model

Hixson Crowell model shows direct proportionality between particle regular area and cube root of volume. The equation governing this model is as under

$M_0^{1/3} - M_t^{1/3} = K_s t$

Where, "M_0" is initial concentration of drug in dosage form while "M_t" is concentration of drug remaining "K_s" shows the surface volume relation. This model assumed that release of drug was governed by the dissolution instead of diffusion (Costa and Sousa Lobo, 2001).

(d) Korsmeyer-pappas plot

Korsmeyer-Pappas plot indicates the mechanism of release of drug. This shows the relation between the natural logarithm of time and natural logarithm of drug release. The equation that governed this model in mentioned

$Q_t/Q_a = K_k t^n$

Where, "Q_t" is amount of drug released at time "t". "Q_a" is amount of drug at time zero, "K_k" is the Korsmeyer Pappas constant and "n" is the release exponent that describes the release mechanism of drug. The value of "n" less than 0.45 show fickian diffusion. The value of "n" between 0.45-0.89 shows the anomalous diffusion. While the value of "n" more than 0.89 shows the super case II relaxation that shows the zero order release (Costa and Sousa Lobo, 2001).

Table 1: Composition of isoniazid sustained-release matrix tablets

Formulation	Isoniazid (mg)	Karaya gum (mg)	Modified karaya gum (mg)	Lactose (mg)	Magnessium Stearate (mg)
F1	150	150	-	442.5	7.5
F2	150	300	-	292.5	7.5
F3	150	450	-	142.5	7.5
F4	150	592.5	-	0	7.5
F5	150	-	150	442.5	7.5
F6	150	-	300	292.5	7.5
F7	150	-	450	142.5	7.5
F8	150	-	592.5	0	7.5

Table 2: Properties of sustained-release granules of isoniazid

Formulation	Angle of repose (θ)	LBD (g/ml)	TBD (g/ml)	Compressibility index	Total porosity	Hausner's ratio	Drug contents (%)
F1	25.743	0.768	0.826	7.017	7.552	1.075	100.23
F2	23.903	0.625	0.765	18.262	22.400	1.223	101.29
F3	26.206	0.625	0.837	25.288	33.920	1.338	100.78
F4	24.663	0.666	0.767	13.103	15.165	1.150	99.80
F5	27.476	0.609	0.833	23.611	36.782	1.313	99.60
F6	29.160	0.625	0.768	19.868	22.880	1.248	99.43
F7	24.496	0.714	0.832	14.242	16.527	1.165	99.22
F8	22.090	0.741	0.773	4.170	4.319	1.043	99.60

Table 3: Properties of sustained-release tablets of isoniazid

Formulation	Weight variation (mg)	Thickness (cm)	Diameter (cm)	Hardness (Kg/cm^2)	Friability (%)	Drug contents (%)
F1	0.933±0.76	0.532±0.007	1.2±0	9.10±0.00	0.335±0.0	100.18±0.03
F2	1.17±0.81	0.558±0.007	1.2±0	8.96±0.057	0.673±0.0	101.28±0.05
F3	1.33±0.96	0.56±0.01	1.2±0	9.90±0.10	0.787±0.195	100.76±0.10
F4	1.152±0.96	0.58±0.008	1.2±0	4.66±0.057	6.756±0.0	99.80±0.01
F5	1.062±0.80	0.506±0.008	1.2±0	10.60±0.00	0.675±0.0	99.60±0.07
F6	0.968±0.57	0.478±0.007	1.2±0	10.53±0.057	0.677±0.0	99.43±0.01
F7	1.012±0.71	0.45±0.008	1.2±0	10.66±0.057	0.00±0.0	99.22±0.2
F8	0.885±0.61	0.425±0.008	1.2±0	10.76±0.057	0.00±0.0	99.63±0.04

Table 4: Comprehensive table for kinetic models

Formulations	Zero order		First order		Higuchi model		Hixson Crowell		Korsmeyer Pappas		
	R^2	K	R^2	K	R^2	K	R^2	K	R^2	N	K
F1	0.95	9.33	0.83	0.18	0.96	46.79	0.94	0.42	0.95	1.14	7.04±1.05
F2	0.91	10.48	0.88	0.22	0.92	52.2	0.95	0.43	0.92	1.30	5.22±0.96
F3	0.98	9.25	0.94	0.22	0.95	45.22	0.87	0.30	0.89	1.23	4.39±0.39
F4	0.96	10.08	0.91	0.23	0.94	0.16	0.94	0.33	0.96	1.40	3.40±0.54
F5	0.98	6.80	0.94	0.11	0.98	33.81	0.95	0.25	0.99	0.66	18.55±0.49
F6	0.95	6.47	0.99	0.11	0.90	31.29	0.84	0.22	0.82	0.63	17.38±1.81
F7	0.99	7.69	0.95	0.15	0.96	37.91	0.92	0.23	0.98	0.94	8.65±0.50
F8	0.98	7.77	0.98	0.17	0.94	37.87	0.93	0.21	0.97	1.01	6.74±0.67

Application of statistics on the dissolution profiles

SPSS 13 was used to apply the one way ANOVA on the dissolution profile of sustained release matrix tablet containing karaya gum and modified karaya gum. Tables of ANOVA, LSD and Dunkens were obtained in the results of SPSS application.

RESULTS

Properties of granules

The properties of sustained-release granules of isoniazid like angle of repose, LBD, TBD, compressibility index, total porosity, Hausner's ratio and drug contents of all formulations are presented in table 2.

Evaluation of physico chemical properties for sustained-release matrix tablets

In vitro evaluation of sustained-release matrix tablets of isoniazid such as weight variation, thickness, hardness, friability, and drug contents were performed. The values of these parameters are presented in table 3.

Swelling and erosion studies

Swelling and erosion studies were performed for all the formulations and presented in fig. 1 and 2 respectively.

***In vitro* dissolution profile for sustained-release matrix tablets**

In vitro drug release was determined by constructing the standard curve of known concentrations of isoniazid. Graphical presentation for dissolution profile of karaya gum and modified karaya gum are depicted in fig. 3 and 4 respectively.

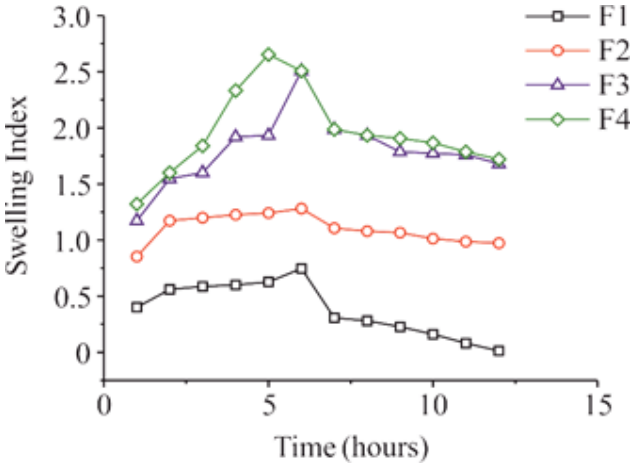

Fig. 1: Swelling and erosion studies of sustained-release formulations of isoniazid having karaya gum

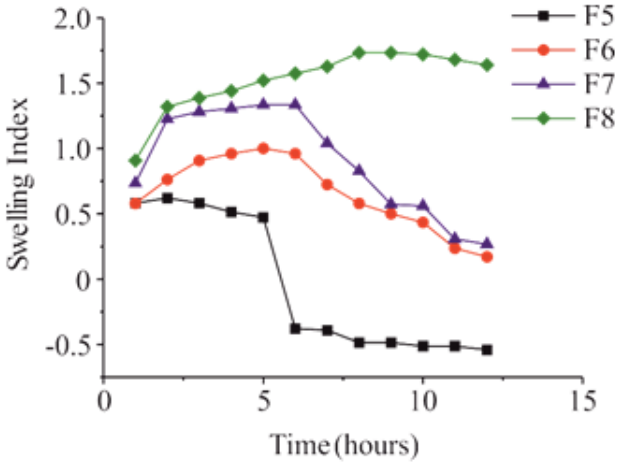

Fig. 2: Swelling and erosion studies of sustained-release formulations of isoniazid having modified karaya gum

Application of release models on dissolution profile

The results of different release models are drawn to check the drug release trend and mechanism. The results of kinetic models of all formulations are presented in table 4.

DISCUSSION

Tuberculosis is a contagious disease with global incidence of 10.4 million and mortality of 1.8 million in 2015. Pakistan is a high TB burden country (5th position globally) with 0.5 million incidence and 46000 mortalities in 2015. Standard TB therapy for nonresistant TB strains consists of four antibacterial drugs with 6 month therapy; isoniazid is one of them. (WHO, 2016a) Patients feel difficulty in adhering TB medication due to multiple dosing, long therapy time, side effects and eradication of symptoms upon therapy. (Munro *et al.*, 2007) Multiple dosing is directly related to patient noncompliance which may lead to MDR- TB thus making treatment options more costly with increased mortality rates. To address the issue of non-compliance by multiple dosing regimens, we formulated sustained-release isoniazid tablet by using karaya gum and cross linked karaya gum. It is a natural gum drived from sterculia tree with no harmful effects on humans and consists of partially acetylated polymer of rhamnose, galactose and glucuronic acid. (Bhardwaj *et al.*, 2000; Eastwood *et al.*, 1983) Both the formulations were evaluated for their physico-chemical characteristics and *in vitro* release profile.

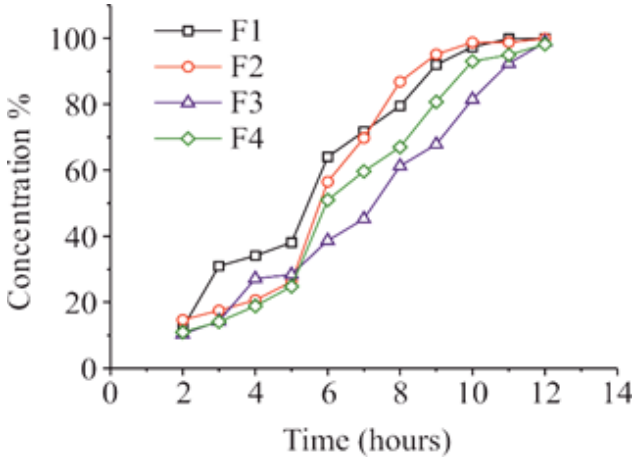

Fig. 3: Dissolution profile for sustained-release tablets having karaya gum

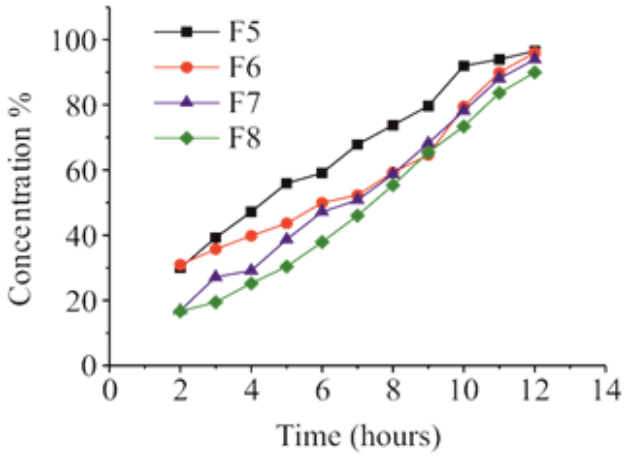

Fig. 4: Dissolution profile for sustained-release tablets having modified karaya gum

Granules were prepared by wet granulation method using 10% starch paste. (Krishnaiah *et al.*, 2002) The granules were apparently good and their color varied from white to very light brown. Lowest value for angle of repose was 22.09 for F8, while the highest value was 29.16 for F6. Granules having value of angle of repose less than 30

show the good flow properties (Reddy *et al.*, 2003). Hence, value of angle of repose for granules of sustained-release matrix tablet was within acceptable range. LBD was ranged between 0.60 (F5) to 0.76 (F1) which was in acceptable limit while TBD was ranged between 0.76 (F2) and 0.83 (F3). It is generally accepted that the high bulk density fills the weight in die of tablet punch machine so it is considered favorable. Compressibility index of all the formulations were between 4.17% (F8) and 25.22% (F3). Low compressibility index (□30%) also indicates good flow property. Hausner's ratio for granules of all the eight formulations was between 1.04 (F8) to 1.33 (F3). The hausner's ratio is usually interconnected with compressibility index and its value less than 1.18 shows the good flow properties (Reddy *et al.*, 2003). Total porosity of all the formulations were between 4.31 (F8) and 33.92 (F3). Less than 48% of total porosity indicates that powder is granulated while more than 48% indicates that it is aggregated (Reddy *et al.*, 2003). So, all the values are within acceptable range. Drug contents of all the formulations were ranged between 99.22% (F7) to 101.29% (F2) which were in acceptable range according to USP specifications. Since all the properties of granules were within acceptable limits so granules were considered suitable for preparation of tablets.

After physico-chemical evaluation of granules, about 100 tablets were prepared for all eight formulations by using single punch tablet machine. Each tablet contained 150mg of isoniazid and net weight of each tablet was 750mg. The tablets were plain, white to very light brown in color and good in appearance. Weight variation of the all the tablets differ between 0.88-1.33% which was in the acceptable limits of ±5% (Emami *et al.*, 2010). Tablet thickness for different formulations was varied between 0.42-0.58cm which was dependent on compressibility index and total porosity of the granules. Moreover, the force of tablet machine also affects the thickness of the tablets and it is inversely proportional to uniformity of granules (Reddy *et al.*, 2003). The diameters of the tablets were quite uniform and it was 12mm. Hardness of tablets was ranged between 4.66-10.76 and was in acceptable limits. The friability is another parameter to check the strength of tablet and it should be less than 1%. All the formulations passed friability test except F4 which has friability value of 6.75%. The drug contents for all the formulations ranged between 99.22-101.28% and were according to USP specifications.

Swelling and erosion behavior was varied among different formulations. F1, F2 and F3 exhibited increase in swelling for first 6 hours and then showed decreased swelling with 0.79, 1.28 and 2.50 were the highest values for the swelling index respectively. F4 showed increase in swelling index till 5 hours (2.65) followed by a decrease. F5, F6, F7 and F8 showed increase in swelling index until 2, 5, 5 and 8 hours respectively. There was equilibrium in swelling index value at 5 and 6 hour for F7 and at 8 and 9 hour for F8. The highest value for swelling index of F5, F6, F7 and F8 was 0.62, 1, 1.33 and 1.73 respectively. None of the formulation fully eroded until 12 hours. It is evident that swelling index was increased with the increasing concentrations of gum. This behavior is due to formation of gel. Cross-linked karaya gum showed earlier erosion than normal karaya gum due to less gum used but its overall dissolution profile showed better behavior due to less dose dumping as observed previously (Reddy *et al.*, 2012).

The drug release profile for formulations having karaya gum was determined and release models were applied. F1, F2, F3 and F4 released 79.50, 86.83, 61.27, 67.01% of isoniazid respectively, within 8 hours while 99% of isoniazid was released from all the formulations having karaya gum within 12 hours. F3 showed comparatively better results as a sustained release formulation with karaya gum. The phenomenon behind the dissolution of tablets having swellable polymer is attributed to the formation of gel on surface of the tablet when in contact with dissolution medium. The drug is then diffused from the matrix system to the dissolution medium. So hydration, swelling and diffusion are main steps for dissolution of drugs (Emami *et al.*, 2010). Higuchi model governed the release of F1 while F2 followed Hixon Crowell model. F3 and F4 followed the zero order concentration independent release. The value of Korsmeyer Pappas model is more than 0.89 for all the formulations having karaya gum which exhibited drug release mechanism super case II (Costa and Sousa Lobo, 2001). It was observed with the increasing concentration of karaya gum the release retarding effect of the formulation was also increased.

F5, F6, F7 and F8 showed 74%, 59%, 59%, 55% of isoniazid release respectively, during 8 hours and 96%, 96%, 94% and 90% within 12 hours respectively. The modified karaya gum showed better results and drug release rates were linear in comparison to karaya gum formulations. The underline reason can be cross linking property of trisodium trimetaphosphate which inhibited the abrupt dose dumping and dose release (Reddy *et al.*, 2012). The dose of isoniazid for F8 was expected to further release in 2-3 hours. F5 was governed by zero order release and Higuchi model. F6 observed first order release while F7 and F8 observed zero order drug release. The n value of Korsmeyer Pappas model showed that F5 and F6 formulations obeyed the anomalous diffusion while F7 and F8 followed the super case II release (Mehsud *et al.*, 2016). Zero order release was the ideal release model for sustained release formulation and was complied by F5, F7 and F8 of the modified karaya gum formulations. The values of ANOVA and LSD indicated that the formulations containing karaya gum were significantly different to each other. Only F3 and F4

showed insignificant difference at 2 and 3 hours which indicates with increasing polymer concentration drug release was retarded. Same was also true for modified karaya gum and only F7 and F8 showed insignificant difference at 2 and 9 hours which indicates increased polymer concentration decreased the drug release. This decreased release and prolonged availability of isoniazid can be of beneficial effects. Since, it is metabolized by acetylation and in slow acetylators drug can accumulate and cause toxic effects such as neuro and hepatotoxicity (Preziosi, 2007), but if isoniazid is released slowly the enzyme saturation can be avoided. Nonetheless, this is a hypothesis only and we were unable to provide experimental evidence for isoniazid however same has been observed by other researchers for paracetamol. (Chiew *et al.*, 2010).

CONCLUSION

Cross linking of karaya gum with trisodium trimetaphosphate improved drug release retarding activity and was considered better release retardant as compared to karaya gum. Since, formulation 8 containing modified karaya gum with 1:4, drug to gum ratio showed the better release profile with 90% of drug release in the 12 hours and expected release of 100% in 15 hours.

ACKNOWLEDGMENT

We are thankful to Mr. Naeem Aamir and Miss Saleha Khalid for providing technical assistance.

REFERENCES

Bhardwaj TR, Kanwar M, Lal R and Gupta A (2000). Natural gums and modified natural gums as sustained-release carriers. *Drug Dev. Ind. Pharm.,* **26**(10): 1025-1038.

Bose A, Wong TW and Singh N (2013). Formulation development and optimization of sustained release matrix tablet of Itopride HCl by response surface methodology and its evaluation of release kinetics. *Saudi Pharm. J.,* **21**(2): 201-213.

Burman WJ, Cohn DL, Rietmeijer CA, Judson FN, Sbarbaro JA and Reves RR (1997). Noncompliance with directly observed therapy for tuberculosis. Epidemiology and effect on the outcome of treatment. *Chest,* **111**(5): 1168-1173.

Chiew A, Day P, Salonikas C, Naidoo D, Graudins A and Thomas R (2010). The comparative pharmacokinetics of modified-release and immediate-release paracetamol in a simulated overdose model. *Emerg. Med. Australas,* **22**(6): 548-555.

Costa P and Sousa Lobo JM (2001). Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci.,* **13**(2): 123-133.

Coviello T, Matricardi P, Marianecci C and Alhaique F (2007). Polysaccharide hydrogels for modified release formulations. *J. Control Release,* **119**(1): 5-24.

Eastwood MA, Brydon WG and Anderson DM (1983). The effects of dietary gum karaya (Sterculia) in man. *Toxicol. Lett.,* **17**(1-2): 159-166.

Elkhodairy KA, Hassan MA and Afifi SA (2014). Formulation and optimization of orodispersible tablets of flutamide. *Saudi Pharm. J.,* **22**(1): 53-61.

Emami J, Tajeddin M and Ahmadi F (2010). Preparation and In Vitro Evaluation of Sustained-Release Matrix Tablets of Flutamide Using Synthetic and Naturally Occurring Polymers. *Iran J. Pharm. Res.,* 7(4): 247-257.

Gohel MC and Sarvaiya KG (2007). A novel solid dosage form of rifampicin and isoniazid with improved functionality. *AAPS PharmSciTech.,* **8**(3): E68.

Hiremath PS and Saha RN (2008). Controlled Release Hydrophilic Matrix Tablet Formulations of Isoniazid: Design and In Vitro Studies. *AAPS PharmSciTech.,* **9**(4): 1171-1178.

Krishnaiah YSR, Karthikeyan RS, Gouri Sankar V and Satyanarayana V (2002). Three-layer guar gum matrix tablet formulations for oral controlled delivery of highly soluble trimetazidine dihydrochloride. *J. Control Release,* **81**(1-2): 45-56.

Mehmood Y, Riaz H, Yousaf H, Raza SA, Mahmood RK, Khan ZM and Saleem N (2016). Formulation and in vitro evaluation of colchicines and naproxen sodium sustain release tablets in combination for treatment of gout. *Pak. J. Pharm. Sci.,* **29**(5): 1579-1586.

Mehsud SU, Khan GM, Hussain A, Akram M, Akhlaq M, Khan KA and Shakoor A (2016). Controlled release matrix tablets of glipizide: Influence of different grades of ethocel and Co-excipient on drug release. *Pak. J. Pharm. Sci.,* **29**(3): 779-787.

Moin A and Shivakumar H (2010). Formulation of Sustained-Release Diltiazem Matrix Tablets Using Hydrophilic Gum Blends. *Trop. J. Pharm. Res.,* **9**(3): 283-291.

Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A and Volmink J (2007). Patient adherence to tuberculosis treatment: A systematic review of qualitative research. *PLoS Med,* **4**(7): e238.

Preziosi P (2007). Isoniazid: metabolic aspects and toxicological correlates. *Curr. Drug Metab.,* **8**(8): 839-851.

Reddy KR, Mutalik S and Reddy S (2003). Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. *AAPS Pharmscitech,* **4**(4): 480-488.

Reddy MM, Reddy JD, Moin A and Shivakumar H (2012). Formulation of sustained-release matrix tablets using cross-linked Karaya gum. *Trop. J. Pharm. Res.,* **11**(1): 28-35.

Varshosaz J, Tavakoli N and Kheirolahi F (2006). Use of hydrophilic natural gums in formulation of sustained-

release matrix tablets of tramadol hydrochloride. *AAPS PharmSciTech.,* **7**(1): E168-E174.

WHO. (2015). *Stop Tuberculosis*. Available at: http://www.emro.who.int/pak/programmes/stop-tuberculosis.html [Accessed 18-10-2016].

WHO. (2016a). *Global Tuberculosis Report 2016*. Available at: http://www.who.int/tb/publications/global_report/en/ [Accessed 29.10.2016].

WHO. (2016b). *Tuberculosis*. Available at: http://www.who.int/mediacentre/factsheets/fs104/en/ [Accessed 18-10-2016].