IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF INLAY TABLET ISONIAZID AS SUSTAIN RELEASE AND RIFAMPICIN AS IMMEDIATE RELEASE

Mr. Pradeep Dhanaji Jadhav. Prof K.N Tarkase and Prof N.S Pawar.

Dept. of Quality Assurance/ Masters in pharmacy Dr.Vitthalrao Vikhe Patil Foundation's Collage of Pharmacy, Ahmednagar, Savitribai Phule Pune university/ INDIA

ABSTRACT:

The present research endeavor is directed towards the development of inlay tablets of Isoniazid as sustained release and Rifampicin as immediate release. All the formulations were evaluated for physical characteristics, disintegration, In Vitro dissolution study and stability study. Following conclusions have been made from the present study.

The possibility of drug excipients interaction was investigated by FTIR. The physical characteristics of all the blended formulations were satisfactory. The prepared tablets of sustained release and immediate release were evaluated for assay, weight variation, hardness, thickness, friability and disintegration time and results were found to be within official limits.

The disintegration studies showed that immediate release formulation using crosscarmellose sodium and Sodium Starch Glycolate was best disintegrating within 3 Min.

The In Vitro dissolution studies were performed for all the IR formulations. Among all the formulations, F8 containing Croscarmellose Sodium, Sodium Starch Glycolate and PVP K30 showed fastest release i.e97.68% of drug in 30 mins.

In Vitro dissolution study of Sustained release formulations was performed and release profile of formulation F8 containing 25% of concentration of HPMC K100 M and 22% of Ethyl cellulose was best when compared to other eight formulations

The stability study was conducted for 3 months under room temperature and 40 °C . Finally after the duration, the product was analyzed for physical appearance, disintegration time etc. The results obtained

were found to be within the specification limits.

Thus from the results of the present study it was concluded that anti-tubercular drugs with different mechanism of action formulated as inlay tablet improved antitubercular activity by releasing drug up to 12 hours and thereby reducing frequency of administration and improvingpatient compliance.

Keywords:

WHO – World Health Organization, SSG – Sodium Starch Glycolate, FTIR –Fourier Transform Infrared Spectroscopy, NADH - Nicotinamide Adenine Dinucleotide

1. INTRODUCTION

1.1 Therapeutic agent/ Drug [1-5]

It is the single active chemical entity present in the medicine that is used for diagnosis, prevention, treatment or cure of a disease. This disease oriented definition of a drug does not include contraceptives or use of drugs for improvement of health. The WHO (1966) has given a more comprehensive definition "Drug is any substance or product that used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipients". The term drug is being also used to mean, addictive, abuse substances. Drug should refer to a substance that has some therapeutic or diagnostic applications.

The WHO has defined Essential Drugs (Medicines) as "those that satisfy the priority healthcare needs of the population." Essential medicines are intended to be available within the context of functioning health system at all times and in adequate amounts, in appropriate dosage forms,within assured quality.

1.2 Routes of Drug Administration

Various routes with Respective formulations

Table 1: Various Routes with Respective Formulation

Sr. No.	Routes of Administration	Formulations
1	Topical	Gel, Ointment, Cream, Transdermal Patch
2	Oral	Solution, Suspension, Emulsion, Tablet, Capsule
3	sublingual	Tablet
4	Rectal	Suppository, Enema
5	Cutaneous	Injection

Sr. No.	Routes of Administration	Formulations
6	Inhalation	Inhaler, Spray
7	Nasal	Nasal Drop
8	Parenteral	Injection

Factors governing choice of route

- Physical and chemical properties of drug like solid, liquid, gas, solubility, stability, pH,irritancy.
- Site of desired action that may be localized and approachable or generalized and notapproachable.
- Rate and extent of absorption of the drug from different routes.
- Effect of digestive juices and first pass metabolism of drug.
- Rapidity with which the response is desired.
- Accuracy of dosage required.
- Condition of the patient .

1.4 Tablet [6, 7]

Tablets are defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either compression or molding methods. Tablets remain popular because of the advantages afforded both to the manufacturer (eg: simplicity and economy of preparation, stability and convenience in packaging, shipping and dispensing) and the patient (eg: accuracy of dosage, compactness, portability). They vary in shape, size and weight depending upon the amount of drug substance present and the intended method of administration. It is the most popular dosage form and 70% of the total medicines are dispensedin the form of tablets.

Advantages of tablets

1. They are a unit dose form, and they offer the greatest capabilities of all oral dosage formsfor the greatest dose precision and the least content variability.
2. Their cost is lowest of all oral dosage forms.
3. They are the lightest and most compact of all oral dosage forms.
4. They are in general the easiest and cheapest to package and ship of all oral dosage forms.

Disadvantages of tablets

1. They are difficult to swallow in case of pediatric, geriatric, unconscious patients.

2. Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.

3. Drugs with poor wetting, sloe dissolution properties, optimum absorption or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.

4. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or coating.

1.6 Inlay Tablets [8]

A variation of the compression coated tablet is the inlay tablet. In the inlay tablet, instead of the core tablet being completely surrounded by the coating, its top surface is completely exposed i.e., only the bottom layer of the coating is deposited in the die and core is placed on it. It is a dosage form comprising of high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release high dose high solubility active ingredient per unit is from 500 mg to 1500 mg and the weight of immediate release active ingredient is up to 50 mg The dosage form consists of two parts, core portion as an immediate release and cup portion as modified release.

- The core portion consists of super disintegrant, low dose drug and excipients.
- The cup portion consists of high dose, high solubility active ingredient, hydrophilic release controlling agent and excipients

1.7 Immediate release tablets [9,10,]

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour1. To enhance dissolution and hence bioavailability of any drug from immediate release tablets, disintegration is one of the important process. Few Super-disintegrants are available commercially as Croscarmellose sodium, Crospovidone and SSG.

1.8 Sustained release dosage form [11]

Conventional drug delivery systems are used in treatment of an acute disease or a chronic disease using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as drug carriers. This type of drug delivery system is known to provide a prompt release of drug. Therefore, to achieve as well as to maintain the drug concentration within therapeutically effective range needed for treatment, it is often necessary to take this type of delivery system several times a day. This results in significant fluctuations in drug levels.

DRUG PROFILE:

Rifampicin [16,17]

- Molecular formula C43H58N4O12

Chemical structure

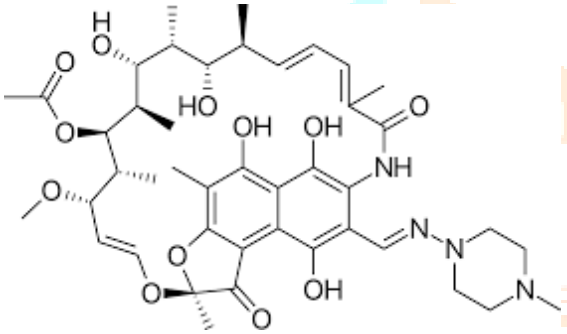


Figure 2: Structure of Rifampicin

- Generic name 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22- heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7 (epoxypentadeca[1,11,13]trienimino)naphthol[2,1-b]furan- 1,11(2H)-Dione 21-acetate
- Molecular weight 822.94
- Solubility Freely soluble in chloroform and DMSO; soluble in ethyl acetate, methanol,tetrahydrofuran; slightly soluble in acetone, water, carbon tetrachloride
- Polarity (Log P) 3.719
- Acidity/basicity pKa 1.7 for the 4-hydroxy and pKa 7.9 for the 3-piperazine nitrogen
- Stability Very stable in DMSO; rather stable in water
- Melting point 183ºC
- Optimal human dosage

  Dose 10 mg/kg, in a single daily administration, not to exceed 600 mg/day, oral or i.v
- *In vitro* potency For *M. tuberculosis* H37Rv, MIC is 0.4 mg/ml

Mechanism of action

Rifampicin inhibits the essential *rpoB* gene product b-subunit of DNA dependent RNA polymerase activity, acting early in transcription (Wehrli *et.al*., 1968). It is thought to bind to the ß-subunit, close to the RNA/DNA channel, and physically blocks the transit of the growing RNA chain after nucleotides have been added

Isoniazid [18,19]

- Molecular formula C6H7N3O

Chemical structure

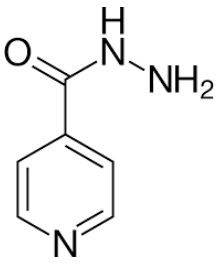


Figure 3: Structure of Isoniazid

- Generic name isonicotinic acid hydrazide; isonicotinoylhydrazine. isonicotinylhydrazine
- Molecular weight 137.14
- Solubility soluble in water (~14% at 25ºC, ~26% at 40ºC) ethanol: (~2% at 25ºC), boilingethanol (~10%), chloroform (~0.1%). Practically insoluble in ether, benzene.
- Polarity (Log P) 0.64
- Acidity/basicity pH of a 1% aqueous solution 5.5 to 6.5
- Stability Very stable in DMSO; rather stable in water
- Melting point 171.4ºC
- Optimal human

Dosage: 5 mg/kg for adults, 10-20 mg/kg for children. Adult dosing generally 300 mg capsule administered orally, once daily; or 15 mg/kg up to 900 mg/day, two or three times/week, ideally Dose administered 1 h before or 2 h after a meal. Concomitant administration of pyridoxine (B6) recommended for malnourished patients, adolescents, and those predisposed to neuropathy (e.g. diabetic).Can also be given intramuscularly or intravenously (WHO, 2003).

1. *In-vitro* potency For *M. tuberculosis* H37Rv, MIC is 0.025 mg/ml.

Mechanism of action

Isoniazid is a prodrug activated by catalase-peroxidase hemoprotein, KatG. Isoniazid inhibits InhA, a nicotinamide adenine dinucleotide (NADH)-specific enoyl-acyl carrier protein (ACP) reductase involved in fatty acid synthesis

Solubility:

This product is soluble in methanol (50 mg/ml), yielding a clear solution.

Appearance:

White/Red crystalline powder.

- **Excipients-**

I. Disintegrating- Croscarmellose.
II. Superdisintegrant- Sodium starch glycolate.
III. Absorb moisture- Talcum.
IV. Good adhesive properties- PVP K 30.
V. Increased hardness – Aerosil
VI. Binder - HPMC K 100 M
VII. Diluent - Lactose

Material and Method :

Equipment used:

FTIR

Make: jasco FT/IR

Software: OPUS 7.5

Attachment: Transmitter, ECO-ATR

UV Spectrophotometer:

Specifications of double beam UV-Visible spectrophotometer

Make: Jasco Model: V-630

Software: Spectra Manager, UV Probe 2.51

Analytical balance:

Make: Shimadzu
Model: BL-22011

Ultrasonicator:

Make: Citizen digital ultrasonicater cleaner

Model: CD-4820

Tablet manufacturing formula for Rifampicin

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rifampicin (60mg)	12%	12%	12%	12%	12%	12%	12%	12%	12%
Lactose (300 mg)	60%	55%	50%	60%	55%	50%	50%	55%	60%
Croscarmellose Sodium (75mg)	15%	20%	25%	-	-	-	20%	10%	5%
Sodium Starch Glycolate	-	-	-	15%	20%	25%	10%	10%	5%
PVP-K30 (50 mg)	10%	10%	10%	10%	10%	10%	5%	10%	15%
Talc (10mg)	2%	2%	2%	2%	2%	2%	2%	2%	2%
Aerosil (5 mg)	1%	1%	1%	1%	1%	1%	1%	1%	1%
Color (q.s.)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total (500 mg)	100%	100%	100%	100%	100%	100%	100%	100%	100%

Tablet manufacturing formula for Isoniazid

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Isoniazid (30mg)	33.3%	33.3%	33.3%	33.3%	33.3%	33.3%	33.3%	33.3%	33.3%
HPMC K 100 M (13.5 mg)	30.%	25%	20%	-	-	-	21%	25%	22%
Ethyl Cellulose (13.5 mg)	-	-	-	30%	25%	20%	21%	22%	15%
Gelatin (9.0 mg)	11%	11%	11%	11%	11%	11%	11%	11%	11%
Starch (22.2 mg)	22%	27%	32%	22%	27%	32%	10%	5%	15%

Talc (0.9 mg)	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Aerosil (0.9 mg)	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
Isopropyl alcohol (IPA)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total (90 mg)	100%	100%	100%	100%	100%	100%	100%	100%	100%

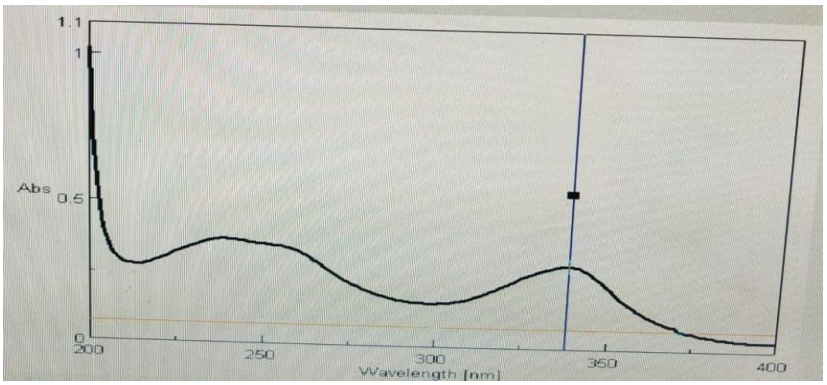
Melting point determination:

Melting point of Isoniazid and Rifampicin was determined using capillary tube method. Observed value of melting points of the two drugs was compared with the reported values.

Sr. No.	Melting PointRange	Isoniazid (API)	Rifampicin (API)
1.	Asper Literature	113^0-115^0 C	212-219 ^{0} C
2.	Practical	115^0 C	214^0 C

Analytical method development of rifampicin (IR) and Isoniazid (SR) by UV spectrophotometer

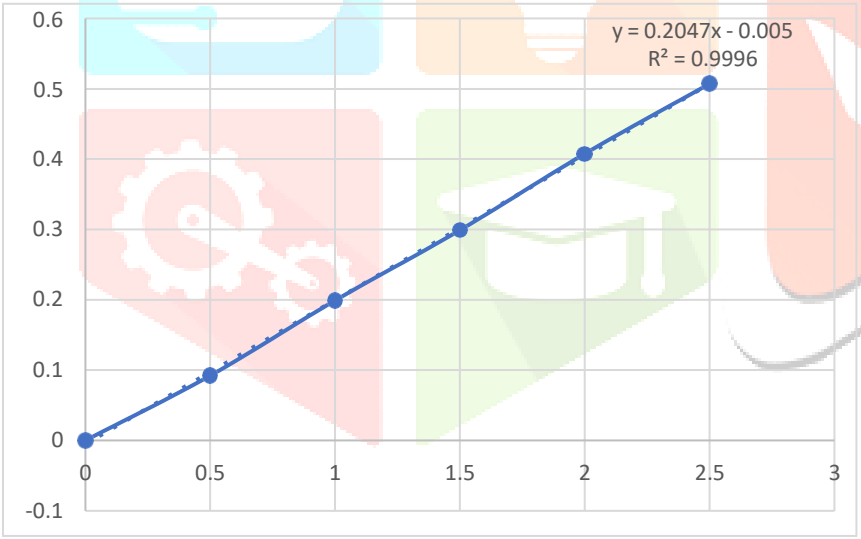
Uv Spectrum of Rifampicin (IR)



λ_{max} of Rifampicin -336

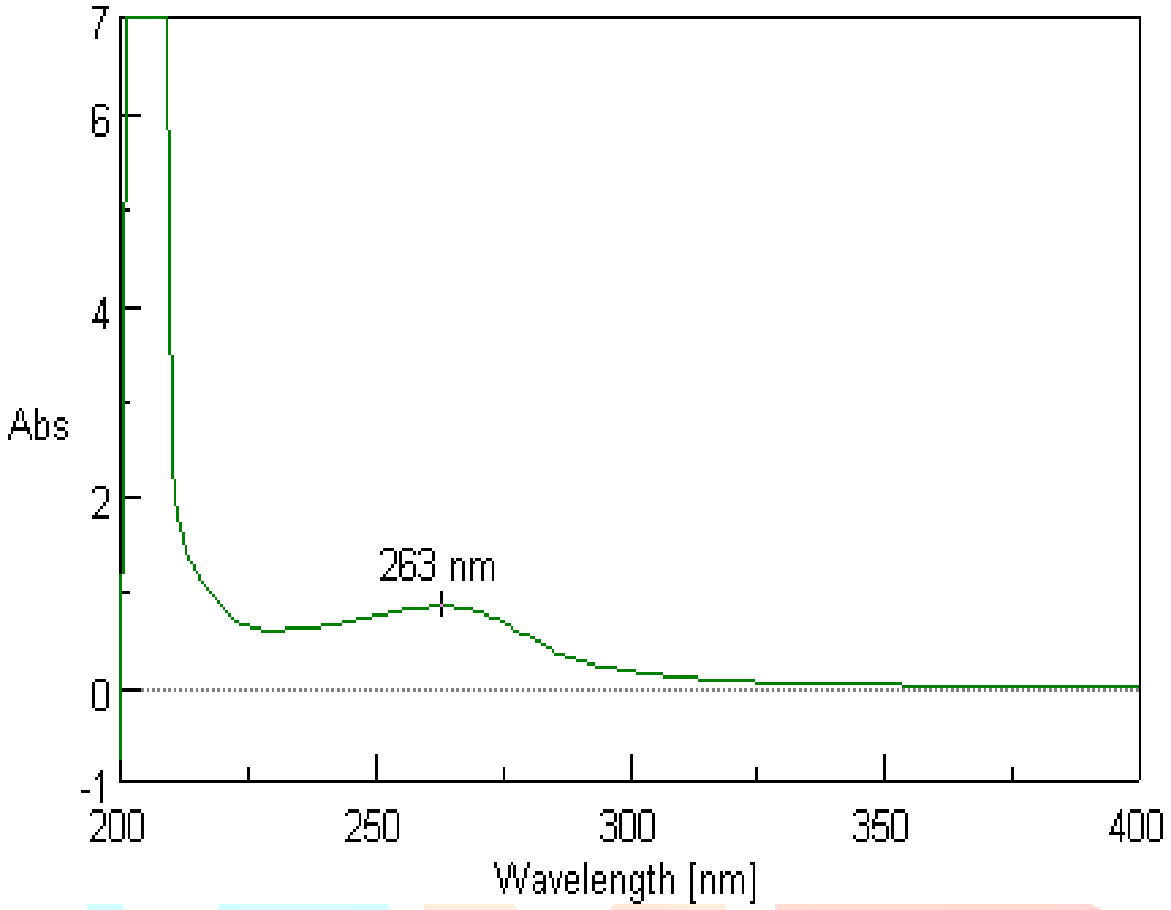
Sr. No.	Concentration (µgm/ml)	Absorbance
1.	0	0
2.	0.5	0.0923
3.	1	0.1991
4.	1.5	0.2991
5.	2	0.4076
6.	2.5	0.5073

Standard curve of Rifampicin in Methanol



Sr. No.	Solvent	Equation	R^2
1.	Methanol	y = 0.2047x - 0.005	0.9996

Ultraviolet Absorbance Spectrum – Isoniazid

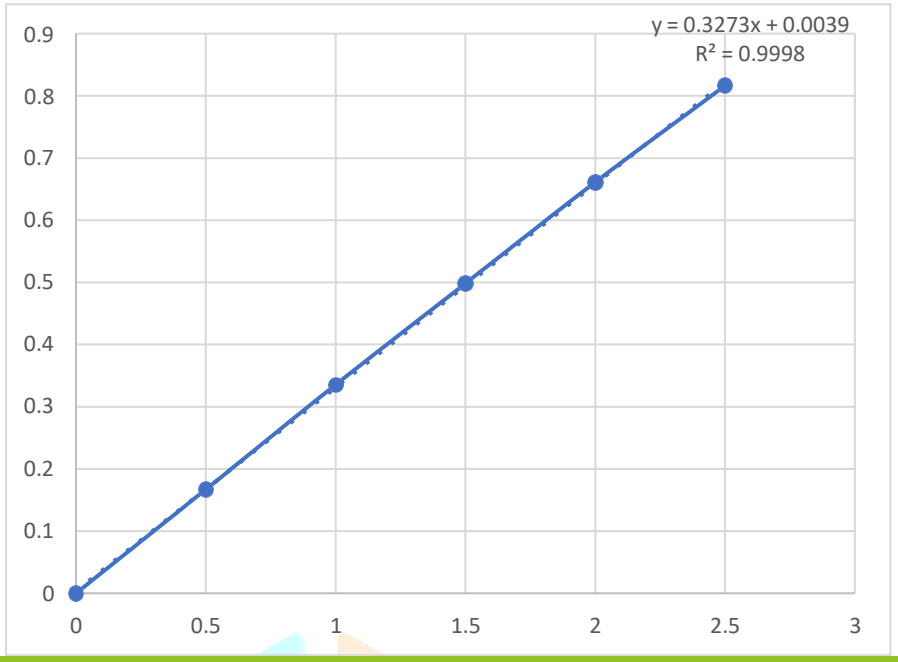


λ_{max} of Isoniazid -263 nm

- **Calibration Curve of isoniazid in Methanol at variousconcentration**

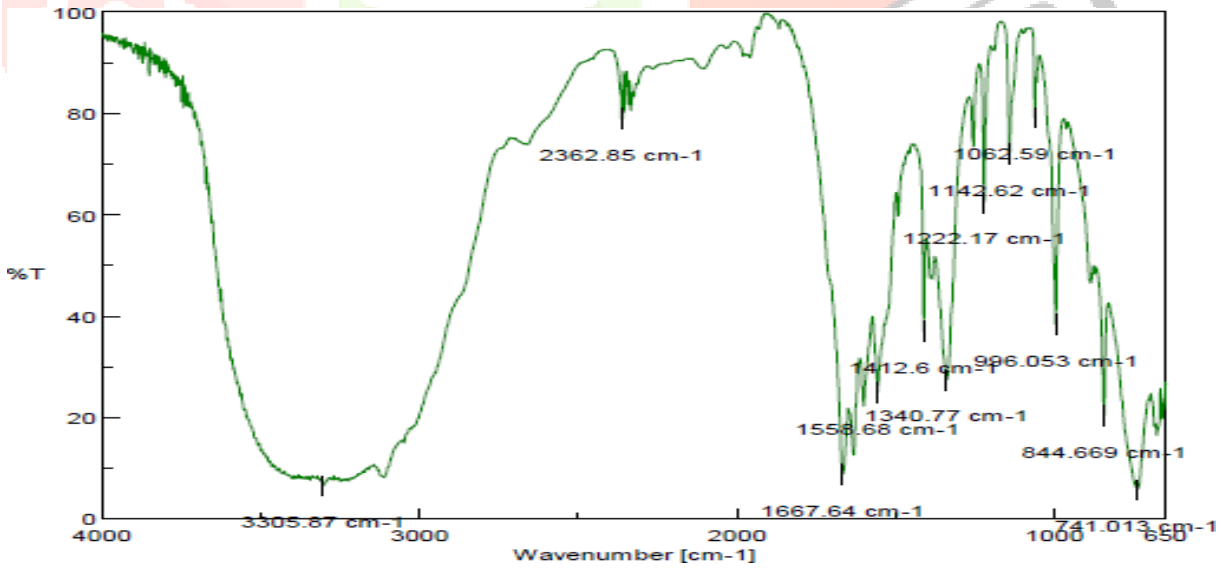
Sr. No.	Concentration (µgm/ml)	Absorbance
1.	0	0
2.	0.5	0.167
3.	1	0.3354
4.	1.5	0.4983
5.	2	0.6612
6.	2.5	0.8164

Standard curve of isoniazid cline in Methanol



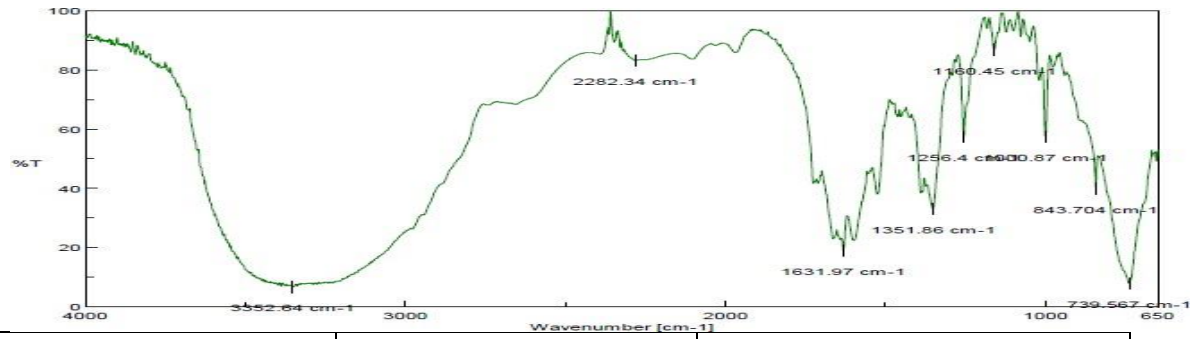
Sr. No.	Solvent	Equation	R^2
1.	Methanol	y = 0.3273x +0.0039	0.9998

Infrared Spectrum of Isoniazid



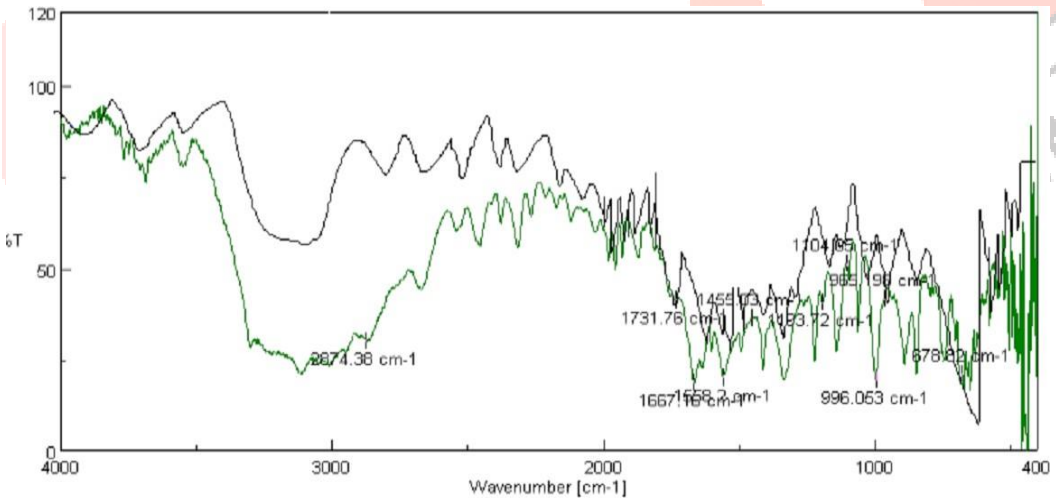
IR Absorption Band (cm -1) (Standard)	IR Absorption Band (cm -1) Observed	Functional Groups present
3300.0 - 2800.0	3300.0 - 2800.0	-NH, -NH bonded stretching
1666.55	1670	-C=O stretching
1631.83	1640	-NH3 asymmetric bending
1552.75	1560	Aromatic ring vibration
1494.88	1500	Aromatic ring vibration

Infrared Spectrum of Rifampicin

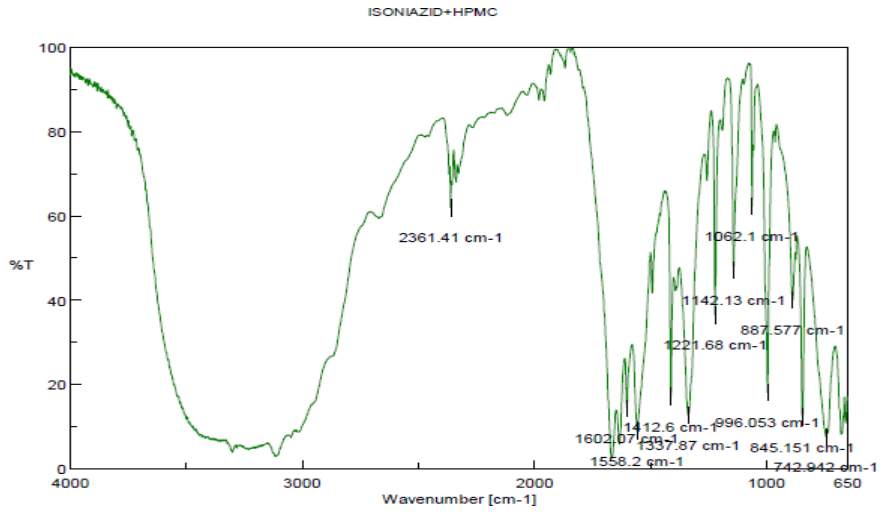


IR Absorption Band (cm -1) (Standard)	IR Absorption Band (cm -1) Observed	Functional Groups present
3416.05 broad peak	3500-3000	-OH stretching
2933.83	2930	-CH3 stretching
2846.1	2820	-CH3O asymmetric stretching
2779.52	2800	-CH3N stretching
1720.56	1715	-C=O acetyl stretching
1647.26	1670	-C=N- asymmetric bending
1560.46	1570	-C=C- stretching
1379.15	1400	-C-N- stretching
1246.06	1255	-C-O-C- acetyl group

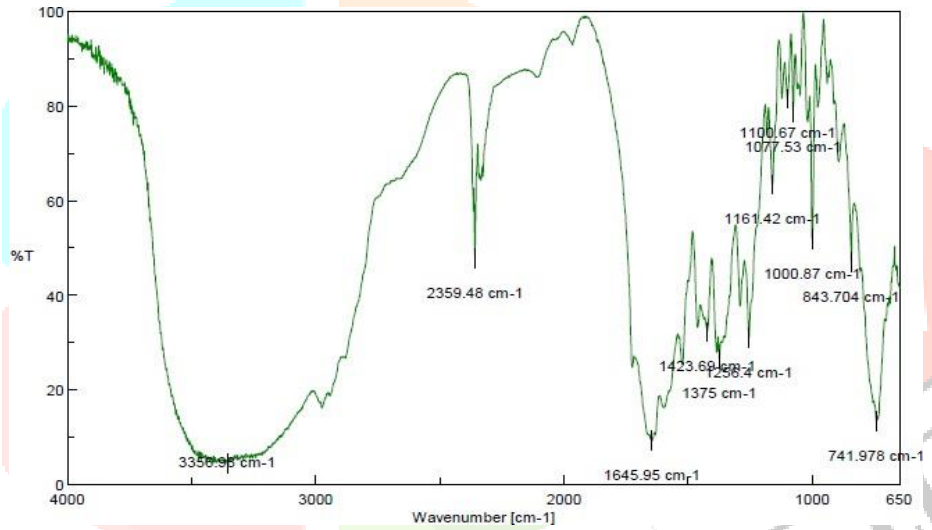
Infrared Spectrum Isoniazid of with Excipient



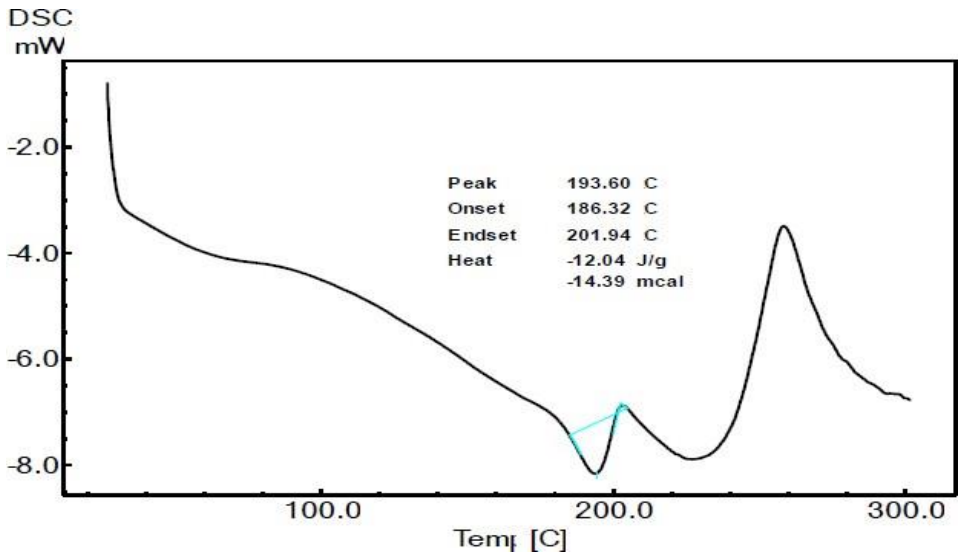
IR spectra of Isoniazid with HPMC K100 M



IR spectra of Rifampicin with PVP-K30

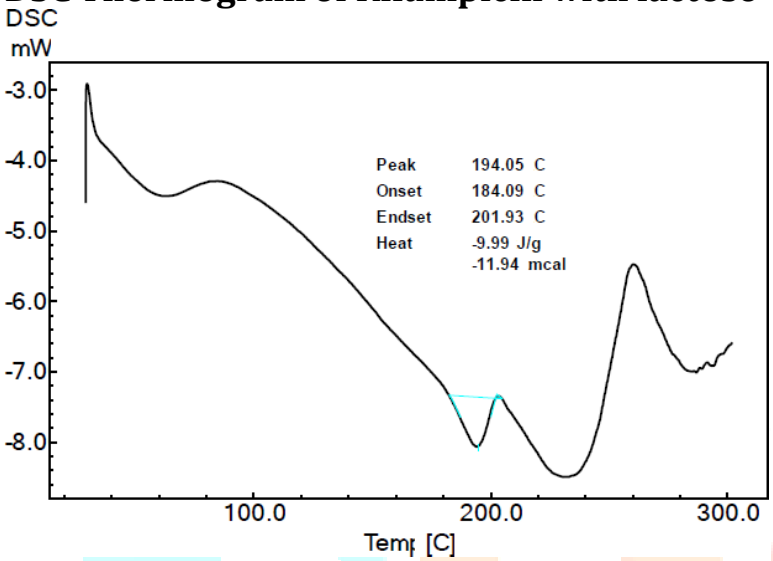


Differential Scanning Colorimetry (DSC) Rifampicin

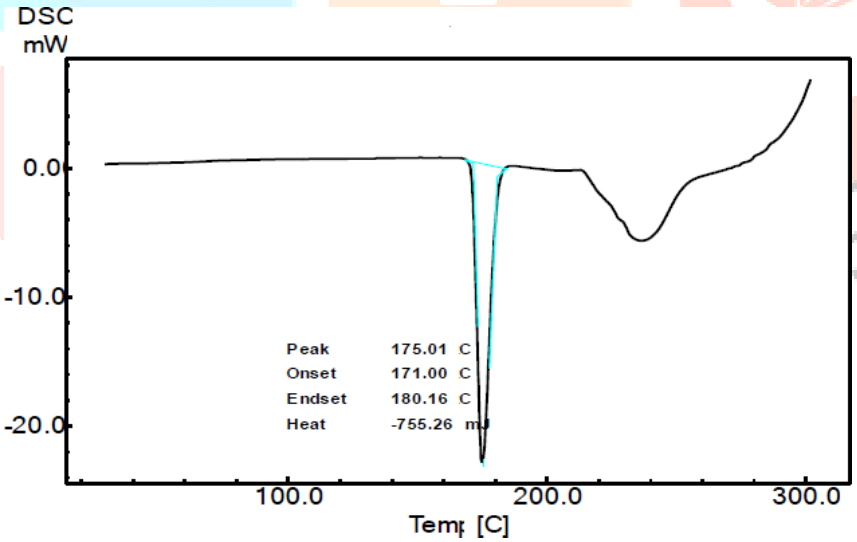


DSC is useful in the investigation of solid state interactions. Thermo grams are generated for pure drugs and mixtures of drug and excipients. From the thermo grams (Figure 22, 23, 24) it is quite clear that there is interaction between the drugs and the excipients as far as the melting point of the drug is concerned From the literature the melting point of rifampicin is observed in the range of 138°C-188°C in the thermogram the rifampicin peak was observed at 186.32°C to 193.60°C which is in the range.

DSC Thermogram of Rifampicin with lactose



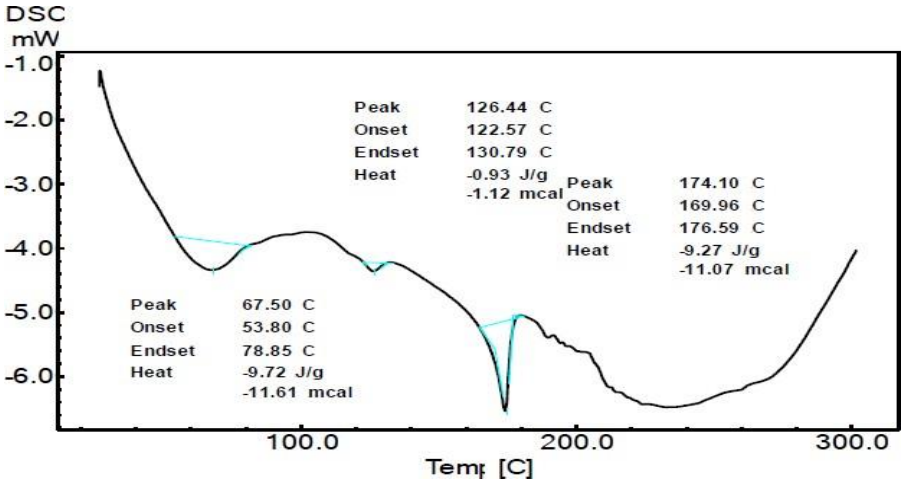
DSC Thermogram of Isoniazid



As per literature the thermogram of Isoniazid was observed at 171.4°C. The above DSCthermogram is observed at 171°C which is similar to the literature.

DSC Thermogram of Isoniazid with HPMC K100 M

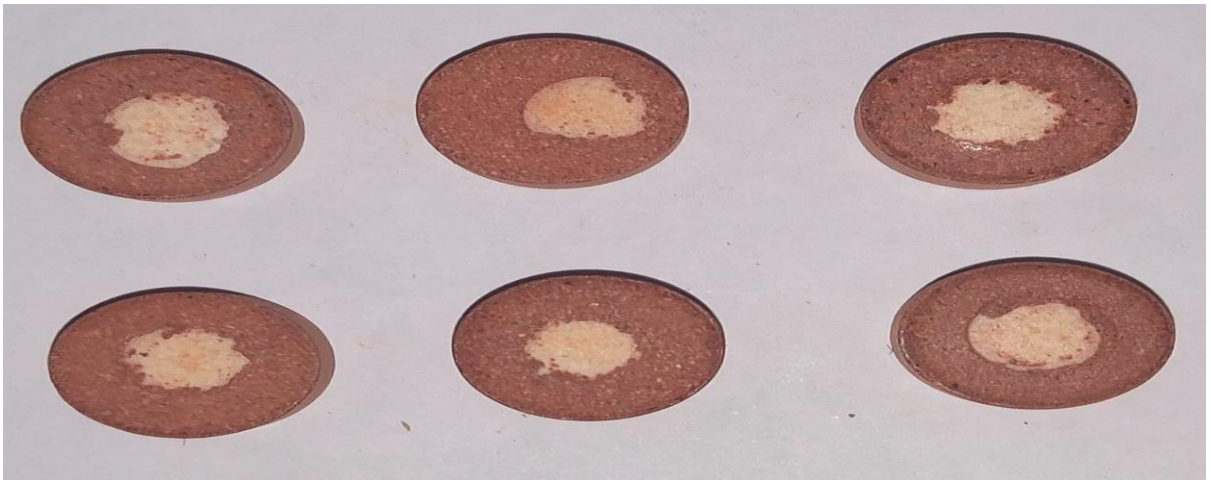
From the DSC thermogram of Isoniazid with HPMC K100 M it was observed that there is nointeraction between Isoniazid and HPMC 100M



Compression of Rifampicin and Isoniazid Inlay Tablet

Compression of Inlay tablet of rifampicin and isoniazid was done in two steps:

1. **Compression of Isoniazid sustained release tablet:** the compression of isoniazid granules was done by using 2 mm round shape punch having plain on both side. The isoniazid tablet is white or cream white in nature.
2. **Compression of Rifampicin immediate release tablet:** the compression of Rifampicin granules was done by using 8 mm punch, the granules have red color. Firstly, the granules of rifampicin was poured in the 8 mm punch and then the tablet of isoniazid was kept in the punch over the rifampicin granules and compressed by using suitable compression force. Final tablet is looking like inner or top section of tablet covered with isoniazid and the around or outer section is of rifampicin. The figure 27 showing the Inlay tablet of rifampicin and isoniazid.



Pre-compression parameter evaluation of Inlay tablet of Rifampicin and Isoniazid

Bulk and Tapped Density

The bulk density of rifampicin was found in the range from 0.499 to 0.522 g/cm3 and tapped density was found in the range from 0.583 to 0.606 g/cm3 whereas, Bulk density of Isoniazid was found in the range of 0.465 to 0.523 g/cm3 and tapped density was 0.574 to 0.614 g/cm3.**Angle of repose (θ)**

The angle of repose of various Rifampicin and isoniazid granules prepared with different polymer was measured by funnel method. Angle of repose was found in the ranges from 24.80° to 26.60°.for Rifampicin and 25.26° to 27.42° so, also evidenced with angle of repose that granules have a good flow property. The results are given in Table 13.

Compressibility index

A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. Values of Carr's Index (Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. The compressibility index of Rifampicin was found in the range

13.8 to 14.6% whereas, Isoniazid compressibility was 13.6 to 14.1 % hence they exhibit good flow property. Data was given in Table 13.

Hausner's ratio

Hausner ratio is an indirect index of ease of powder flow. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25). The Hausner's ratio of Rifampicin and Isoniazid granules prepared with different polymer was calculated by using bulk density and tapped density data. It was found in the range of 1.17 to 1.19 whereas; isoniazid has Hausner ratio ranges from 1.16 to 1.18 which indicates better flow property. The results are given in

Pre-compression parameter of Rifampicin (IR) granules

Formulation	Bulk density* g/cm3	Tapped density* g/cm3	Compressibility index* g/cm3	ausner's ratio*	Angle of repose*
F1	0.516±0.02	0.516±0.02	14.0±0.053	1.19±0.051	24.80±0.111
F2	0.522±0.04	0.606±0.03	14.0±0.02	1.17±0.09	26.20±0.02
F3	0.507±0.03	0.507±0.03	14.0±0.029	1.18±0.009	26.20±0.292
F4	0.499±0.02	0.499±0.02	13.9±0.053	1.19±0.040	25.88±0.433
F5	0.500±0.01	0.500±0.01	14.1±0.003	1.19±0.051	24.80±0.111
F6	0.517±0.08	0.517±0.08	14.1±0.039	1.18±0.028	25.64±0.395
F7	0.513±0.08	0.514±0.08	14.1±0.011	1.19±0.021	26.60±0.105
F8	0.489±0.02	0.492±0.02	13.8±0.012	1.17±0.029	24.80±0.391
F9	0.502±0.01	0.509±0.01	13.7 ±0.010	1.18±0.028	25.62 ±0.390

Pre-compression parameter of Isoniazid (SR) granules

Formulation	k density g/cm3	Tapped density g/cm3	Compressibility index g/cm3	usner'sratio	Angle of repose
F1	0.515±0.03	0.576±0.03	14.0±0.019	1.17±0.042	27.12±0.123
F2	0.523±0.04	0.614±0.04	13.7±0.042	1.18±0.023	27.42±0.112
F3	0.507±0.03	0.610±0.03	14.6±0.032	1.16±0.021	26.12±0.142
F4	0.499±0.02	0.612±0.03	13.4±0.041	1.17±0.018	25.92±0.115
F5	0.500±0.01	0.592±0.01	14.3±0.032	1.18±0.020	26.23±0.124
F6	0.517±0.08	0.578±0.07	13.8±0.018	1.17±0.022	27.36±0.104
F7	0.513±0.08	0.584±0.07	14.5±0.031	1.16±0.041	25.31±0.105
F8	0.502±0.01	0.594±0.02	1.37±0.036	1.16±0.028	25.43±0.112
F9	0.465±0.02	0.574±0.03	13.6±0.039	1.16±0.029	25.26±0.104

Post compression parameter evaluation of Inlay tablet of Rifampicinand Isoniazid

Weight variation

The theoretical average weight Inlay tablet is 590 mg and weight variation of various formulation are depicted in Table15. The percentage deviation of the weight was within 5% asper monograph.

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in **table**

Table 8: Weight Variation Specification as per IP

Average weight of tablet (mg)	% Deviation
80 or less	±10
More than 80 mg but less than 250mg	±7.5
250 mg or more	±5

Friability (F)

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of 6 tablets were placed in the friabilator and were subjected to the 100 revolutions for 4 min. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

F= W initial- W final/W initial ×100

Here,

W initial = Initial weight of tablets

W final = Final weight of tablets

Hardness

The hardness of all batches of Inlay tablet was shown in **Table**. The hardness of the tablet was found in the ranges from 6.4 to 6.6 Kg/cm2. So, it was the sufficient hardness for tablet coating, transporting and packing.

Formulation	Weight variation*	Hardness* (Kg/cm2)	Thickness* (mm)	Friability* (%)	Disintegration Time(Min) (IR)
F1	590±4.15	7.2±0.255	5.3±0.113	0.12±0.102	5 Min 24sec
F2	588±4.86	7.00±0.491	5.2±0.017	0.21±0.026	4 Min 85sec
F3	591±5.62	7.00±0.204	5.3±0.129	0.34±0.034	5 Min 32sec
F4	593±4.12	7.65±0.258	5.1±0.092	0.39±0.045	6 Min 20sec
F5	591±6.24	6.81±0.273	5.1±0.089	0.24±0.019	5 Min 21sec
F6	588±6.29	7.16±0.418	5.2±0.214	0.31±0.040	5 Min 48sec
F7	587±4.56	6.94±0.514	5.2±0.212	0.15±0.025	6 Min30sec
F8	590±5.94	7.00±0.324	5.1±0.091	0.16±0.029	5 Min 03sec
F9	592±4.23	7.67±0.253	5.3±0.128	0.28±0.041	5 Min 92sec

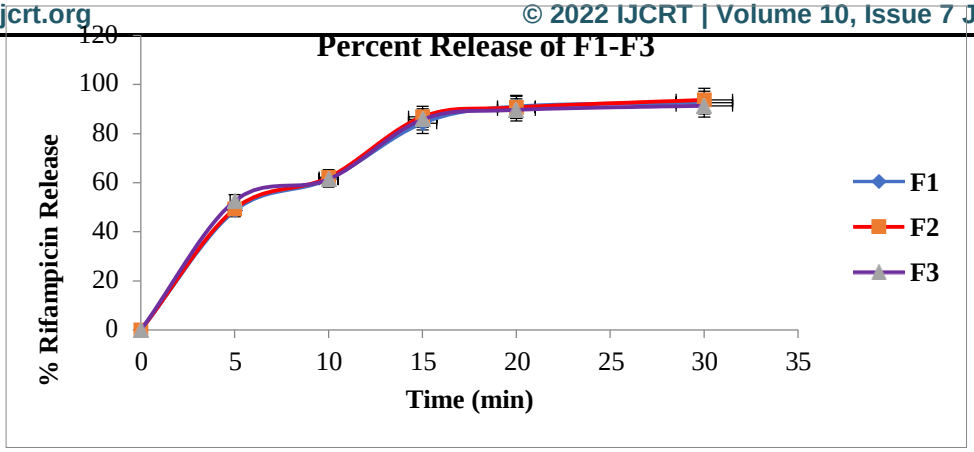
In Vitro Dissolution Study of Rifampicin (IR) from Inlay Tablet

In Vitro Dissolution Study of Rifampicin

Release of the rifampicin at 6 h was considered because from literature it was quite evident that in in vivo conditions the maximum gastroretention that was attained was 5 h. So the study was conducted with the aim to release the drug in the formulations within 6 h. The dissolution study was performed using a USP type II (paddle type) dissolution apparatus at 37 ± 0.5 oC and a paddle speed of 50 rpm. The dissolution testing of optimized formulation was carried out in 900 ml of simulated gastric fluid. At 6 h, 2 ml of sample was withdrawn replacing with fresh medium and the release of rifampicin analyzed at 336 nm using UV-visible spectrophotometer.***In Vitro* Dissolution Study of Isoniazid**

The dissolution study of isoniazid was performed using a USP type I (basket type) dissolution apparatus at 37 ± 0.5 oC and a paddle speed of 50 rpm. The dissolution testing of sustained release tablet was carried out in simulated gastric fluid for the first 2 h and then the medium was changed to simulated intestinal fluid.

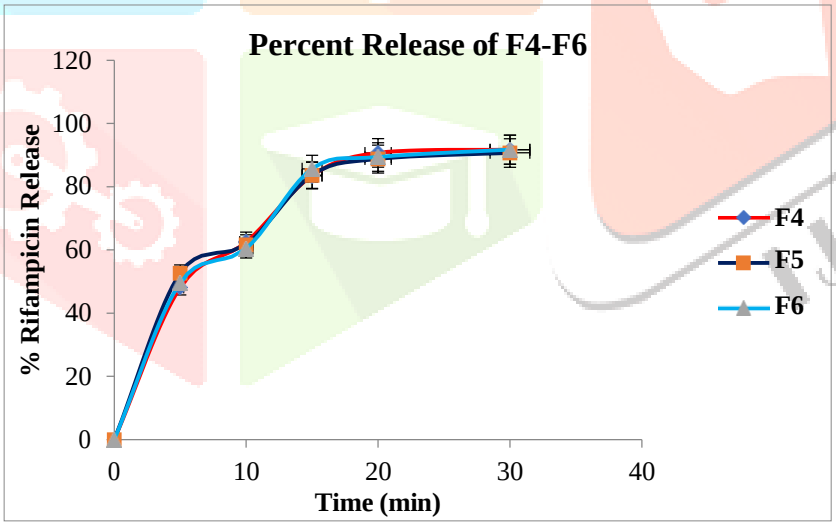
At predetermined time intervals of 1 hr in simulated gastric fluid and 110 min in simulated intestinal fluid, 2 ml of sample was withdrawn replacing with respective fresh medium and the release of isoniazid analysed at 263 nm using UV- visible spectrophotometer.



Percent release of Rifampicin of F1-F3

Time (Min)	% Release of Rifampicin		
	F1	F2	F3
0	0.00	0.00	0.00
5	48.63±1.78	49.36±1.78	52.61±1.78
10	61.48± 1.50	62.18±1.78	61.38±1.78
15	84.27± 1.46	86.87±1.78	85.76±1.78
20	91.04± 1.71	90.67±1.78	89.67±1.78
30	92.64±1.42	93.74 ±1.78	91.34±1.78

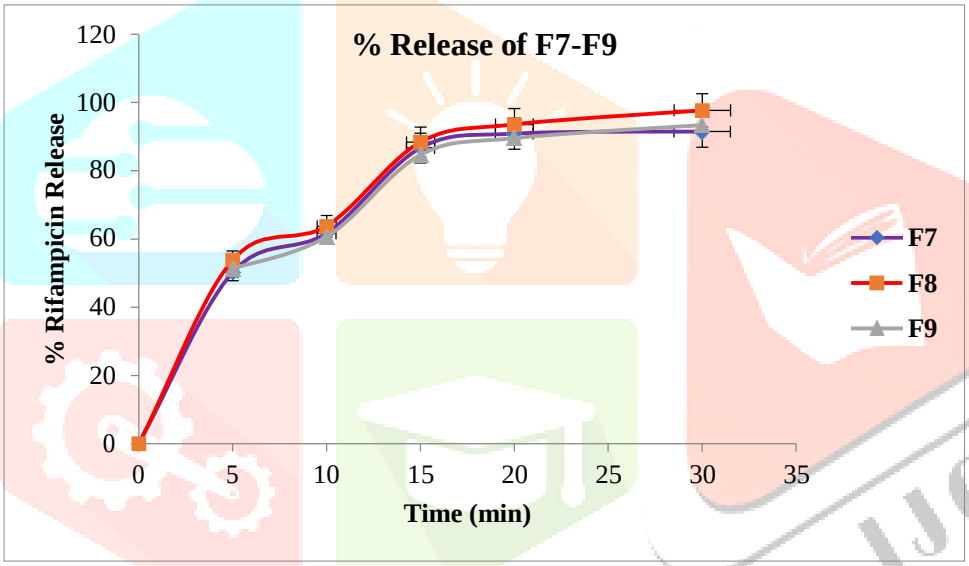
Percent release of Rifampicin from Inlay Tablet of F1-F3



Percent release of Rifampicin of F4-F6

Percent release of Rifampicin of F4-F6

Time (Min)	% Release of Rifampicin		
	F4	F5	F6
0	0.00	0.00	0.00
5	48.15±1.74	52.67±1.72	49.67±1.69
10	62.48± 1.43	61.67±1.62	60.38±1.68
15	83.47± 1.46	83.65±1.73	85.67±1.71
20	90.67± 1.48	88.75±1.75	89.35±1.72
30	91.68±1.40	90.67 ±1.768	91.68±1.68



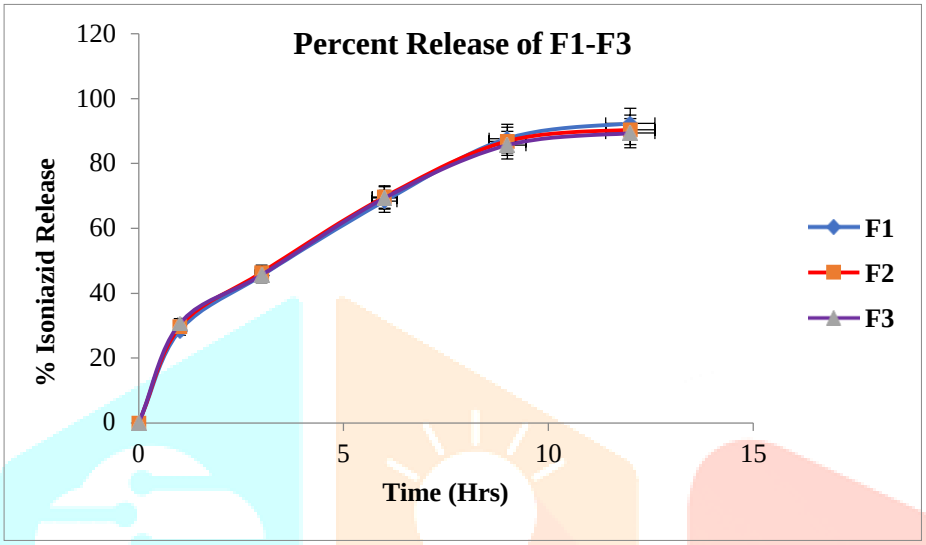
Percent release of Rifampicin of F7-F9

Percent release of Rifampicin from Inlay Tablet of F7-F9

Time (Min)	% Release of Rifampicin		
	F7	F8	F9
0	0.00	0.00	0.00
5	50.24±1.68	53.84±1.63	51.38±1.67
10	61.68± 1.67	63.76±1.65	60.68±1.67
15	86.67± 1.72	88.37±1.72	84.68±1.73
20	90.87± 1.73	93.57±1.71	89.58±1.71
30	91.45±1.71	97.68±1.72	93.40±1.71

From the dissolution study of Rifampicin from the Inlay tablet, it was found the F8 batch is most successful. Which consisting of all excipient with minimum concentration. So, there will be a collaborative effect of all inactive ingredient from the formulation was observed. Croscarmellose sodium, sodium starch glycolate and PVP k30 has more impact on the releaseof rifampicin.

In Vitro Dissolution Study of Isoniazid (SR) from Inlay Tablet

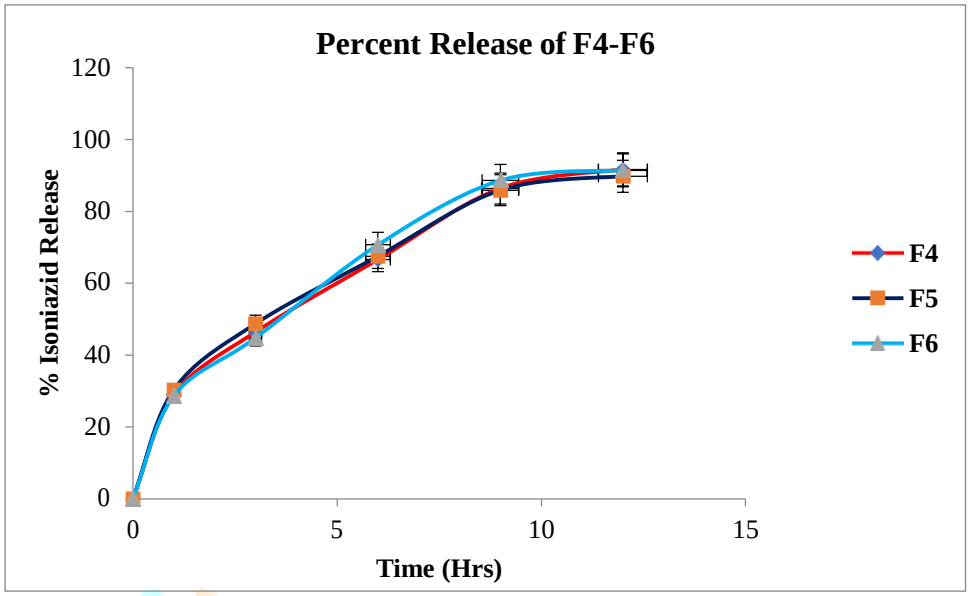


Percent release of Isoniazid of F1-F3

Percent release of Isoniazid from Inlay Tablet of F1-F3

Time (Hrs)	% Release of Isoniazid		
	F1	F2	F3
0	0.00	0.00	0.00
1	28.47±0.37	29.67 ±0.36	30.67±0.46
3	45.47±0.61	46.37±0.52	45.67±0.41
6	68.37±0.52	69.67±0.45	69.37±0.38
9	87.68±0.63	86.87±0.48	85.67±0.53
12	92.35 ±0.53	90.38 ±0.56	89.37±0.48

Percent release of Isoniazid of F4-F6



Percent release of Isoniazid of F4-F6

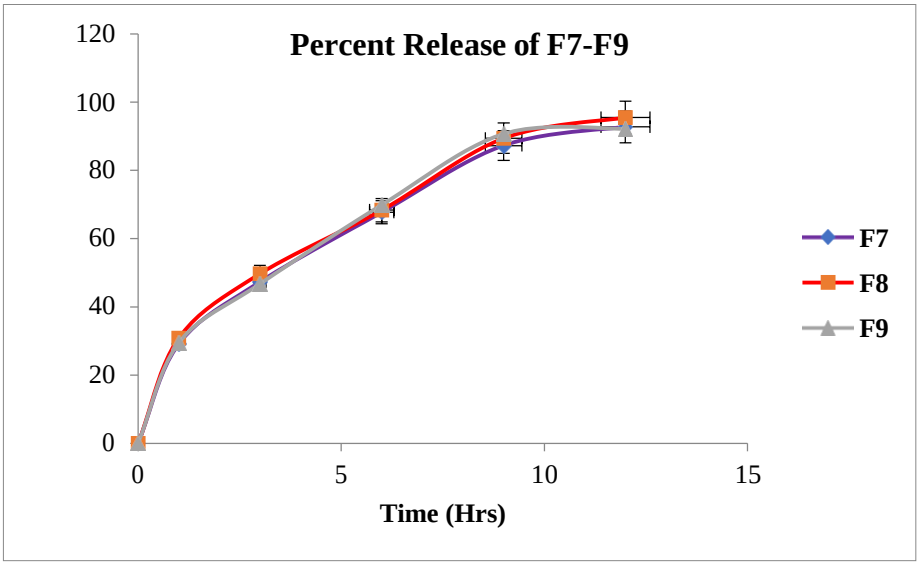
Percent release of Isoniazid of F4-F6

Time (Hrs)	% Release of Isoniazid		
	F4	F5	F6
0	0.00	0.00	0.00
1	28.94±0.47	30.27 ±0.34	28.68±0.41
3	46.38±0.60	48.67±0.53	44.78±0.40
6	66.58±0.53	67.49±0.44	70.68±0.64
9	86.38±0.61	85.89±0.48	88.61±0.42
12	91.67 ±0.51	89.78 ±0.55	91.42±0.43

% Isoniazid Release

Time (Hrs)	% Release of Isoniazid		
	F7	F8	F9
0	0.00	0.00	0.00
1	29.12±0.41	30.84 ±0.35	29.46±0.40
3	47.29±0.62	49.71±0.54	46.71±0.42
6	67.72±0.54	68.37±0.43	69.86±0.62
9	87.29±0.63	89.43±0.45	90.68±0.43
12	92.76 ±0.54	95.48 ±0.52	92.17±0.41

Percent release of Isoniazid from Inlay Tablet of F7-F9



Similarly, like rifampicin release, Isoniazid also releases sustainably from the Inlay tablet. The polymer like HPMC K 100 M and ethyl cellulose plays an important role to sustained the release of Isoniazid. Also, starch is act as binder in the Isoniazid layer which is also gives effect on the release. F8 has better release than other batches.

Stability Study of Inlay Tablet of Rifampicin and Isoniazid

The optimized inlay tablets formulation were subjected to stability studies and results were tabulated in Table

Stability study of Inlay tablet of Rifampicin and Isoniazid

Parameters	One Month		Two Month		Three Month	
	RT	40°C	RT	40°C	RT	40°C
Uniformity of weight (mg)	590.53±1.4	589.76±1.2	590.46 ±1.3	590.68±1.1	588.47±1.2	589.87±1.2
Thickness (mm)	5.1±0.091	5.1±0.090	5.1±0.092	5.1±0.093	5.1±0.092	5.1±0.091
Hardness (kg/cm2)	7.16±0.418	7.08±0.415	7.14±0.406	7.16±0.415	7.17±0.411	7.16±0.419
D.Time(IR) (Min)	5 Min 32sec	5 Min 26sec	5 Min 44sec	5 Min 32sec	5 Min 30sec	5 Min 31sec
Friability (%)	0.34±0.043	0.39±0.045	0.42±0.040	0.38±0.042	0.40±0.045	0.39±0.044

From the stability study of Inlay tablet of Rifampicin and Isoniazid it was conclude that, the optimized or selected formulation 8 (F8) is stable for three month at Room temperature as well as 40°C. The post compression parameter of inlay tablet was found to be stable after the analysis.

CONCLUSION:

The present research endeavor is directed towards the development of inlay tablets of Isoniazid as sustained release and Rifampicin as immediate release. All the formulations were evaluated for physical characteristics, disintegration, In Vitro dissolution study and stability study. Following conclusions have been made from the present study.

The possibility of drug excipients interaction was investigated by FTIR. The physical characteristics of all the blended formulations were satisfactory. The prepared tablets of sustained release and immediate release were evaluated for assay, weight variation, hardness, thickness, friability and disintegration time and results were found to be within official limits.

The disintegration studies showed that immediate release formulation using crosscarmellose sodium and Sodium Starch Glycolate was best disintegrating within 3 Min.

The In Vitro dissolution studies were performed for all the IR formulations. Among all the formulations, F8 containing Croscarmellose Sodium, Sodium Starch Glycolate and PVP K30 showed fastest release i.e97.68% of drug in 30 mins.

REFERENCES

1. Tripathi K.D. Essentials of Medical Pharmacology. 6th ed., Jaypee Brothers MedicalPublishers (P) Ltd; 2008.
2. Rang H.P., Dale M.M., Ritter J.M., Flower R.J.,Rang and Dale's Pharmacology. 6th ed.Elsveier Limited; 2007.
3. Tortora G., Derrickson B., Principles of Anatomy and Physiology. 11th ed., John wiley &sons, Inc: 2006.
4. Lachman L., Lieberman H., kanig J.,The theory and Practice of Industrial Pharmacy. 3rded., Varghese Publishing House: 1987.
5. Verma P., Thakur A., Deshmukh A., Jha A., Verma S., Routes of Administration.International Journal of Pharmaceutical studies and Research. 2010, (1): 54-59
6. Gupta M, Brijesh R. A Review On: Sustained Release Technology. International Journalof Therapeutic Applications. 2012; 8:18-23.
7. Libermann, Lachmann; Pharmaceutical dosage forms- Tablets; Vol 1, P.No:273.
8. Santosh K, Jyoti M; Inlay Tablets: A Novel Approach to Drug Delivery; International journal of advance research pharmaceutical & Biosciences. 2013, 3(2), 127-130
9. Hitesh P Patel, Preeti Karwa, Rama Bukka, Nitesh J. Patel; Formulation and evaluation of immediate release tablets of Zolpidem tartrate by direct compression; mar-apr 2011, Vol 7,Issue 2, article 04, 80-85.
10. Manoranjan Sahu, S.C. Dinda; Formulation and development of modified release inlayered tablet; Journal of pharmacy research 2010, vol 3, issue 4, 794-798.
11. AR Mullaicharam, Ph.Maisa Shummo, P.Muthuprasanna; Sustained Release Matrix Metoprolol Tartrate with Inlay Hydrochlorthiazide Tablet; International Journal of Pharma and Bio Sciences; 2010, Volume 1,

Issue 2, 1-10

12. Alejandro S., Katia S., Julieta C., Novel formulation and drug delivery strategies for the treatment of pediatric poverty-related diseases; Expert Opinion on Drug Delivery 9(3):303-23
13. Ramesh P. Shrutidevi Agrawal, Biopharmaceutic and pharmacokinetic aspects of variable bioavailability of rifampicin; 2004 1;271, 1-4
14. Blomberg, B., Evans, P., Phanouvong, S., Nunn, P., 2002. Informal consultation on 4-drug fixed-dose combinations (4FDCs) compliant with the WHO model list of essential drugs. Geneva: World Health Organization. WHO/CDS/TB/2002.299.
15. Bhutani, H., Mariappan, T.T., Singh, S., 2004 a. A study on the physical and chemical stability of anti-tuberculosis fixed-dose combination (FDC) products under accelerated climatic conditions. Int. J. Tuberc. Lung Dis. 8, 1073-1080.
16. https://en.wikipedia.org/wiki/Rifampicin
17. Hanna Engelberg-Kulka, Ronen Hazan; mazEF: A chromosomal toxin-antitoxin module that triggers programmed cell death in bacteria; Journal of Cell Science 118(Pt 19):4327- 32
18. https://en.wikipedia.org/wiki/Isoniazid
19. Petri, W.A., 2001. Antimicrobial Agents. In: Hardmann, J.G., Limbird, L.E., Gilman, A.G. (Eds.), The Goodman and Gilman‟s: the pharmacological basis of therapeutics. MacGraw Hill Medical Publishing division, New York, 10th ed., pp. 1273-1294.
20. https://en.wikipedia.org/wiki/Polyvinylpyrrolidone
21. Ashish S., Chandraprakash k.; Lactose; In book: Reference Module in Food and Health(pp.509-516) Edition: First Vol. III
22. Bala Srinivasan, Nick Taub, Kamlesh Khunti, Melanie Davies; Diabetes: glycaemiccontrol in type 2; BMJ.
23. Mariana T., Gabriel Hancu, Eleonora Mircia, Imultaneous Determination of Isoniazid andRifampicin By Uv Spectrophotometry; Farmacia 65(2):219-224
24. Lachman, L, Lieberman, H.A, Kanig, L.J., 2009. The Theory and Practice of IndustrialPharmacy. Special Indian ed., CBS Publishers & Distributers Pvt. Ltd., New Delhi