FORMULATION AND EVALUTION OF BILAYER TABLET OF RIFAMPICIN AND ISONIAZID FOR TUBERCULOSIS THERAPY

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ABSTRACT

The aim of present study is to formulate and evaluate the bilayer tablets containing Rifampicin immediate release portion(IR) and isoniazid in the sustained release (SR) portion in order to produce a single tablet containing two different classes of drugs as widely prescribed by doctors and to have better patient compliance. The sustained release layer of Isonaizid was prepared by using the grade of HPMCK100m, and lactose along with other excipients like lactose, magnesium stearate, microcrystalline cellulose & talc by wet granulation technique. The immediate release layer of Rifampicin was prepared by direct compression method. The powders were evaluated for their flow properties and the finished tablets were evaluated for their physical parameters. The drug release study of Rifampicin and Isoniazid were evaluated using USP-programmable (type 2) dissolution test apparatus. The release rate was studied for 45 mins by using 0.01M HCL for 2 hrs and 6.8 phosphate buffer as media a developed UV method. The release rate of Rifampicin from all the formulations was more than 80% at 45 min. In case of HPMCK100m the maximum release we get. Total three trial batches of each drug have been manufactured to optimize and develop a robust and stable formulation, the stability studies of the products also comply with ICH guidelines.

Key words : HPMC, IR,SR,ICH guideline, UV method , USP.

INTRODUCTION:

Now a days various developed and developing countries move towards combination therapy for the treatment of various diseases and disorders requiring long term therapy such as tuberculosis, cancer, HIV/AIDS. Combination therapy have various advantages over mono therapy such as problem of dose dependent side effects is minimized, a low dose combination of two different agents reduces the dose related risk , the addition of one agent may counteract some deleterious effects of other, using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet[1].

The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required , or providing uniform drug delivery. If in were to imagine the ideal drug delivery system, two prerequisites would be required. First, it would be a single dose for duration of treatment, whether it is for weeks or months as with infection, as in tuberculosis. Second , it should deliver the active ingredient directly to the site of action , thereby minimizing or eliminating side effects[2].

Tuberculosis is a ubiquitous highly contagious chronic granulomatous bacterial infection, is a still leading killer of the young adults[3]. It is an un curable disease and hence need a long term therapy for treatment of

the disease with a number of drugs given for about 6 to 8 months. Now a days DOTS therapy is being used for the treatment of the disease. Since the control of tuberculosis by using BCG vaccination is unsatisfactory and hence the only option for the treatment is by the anti-tubercular drugs. As suggested by WHO treatment of tuberculosis and drug resistant cases require multi drug therapy comprising

- An initial phase of Rifampicin, Isoniazide, Pyrazinamide, Ethambutol daily for 2 months.
- A continuation phase of Rifampicin, Isoniazide for a further 4 or 6 months either daily or 3 times per week to be administered.

Therefore the present work is aimed to prepare bilayer tablets containing Rifampicin as immediate release and Isoniazide as sustained release tablets.

Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles which improves patient compliance, prolongs the drug(s) action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug levels[4].

Bilayer tablets are prepared with one layer of drug for immediate release while second later designed to release drug , later, either as second dose or in extended release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is release as initial dose and second layer is maintenance dose or sustained release.

Permeability studies have demonstrated that Rifampicin is well absorbed from the stomach due to its solubility which has been shown to be maximal between pH 1-2, although demonstrating solubility in the gastric environment is comparatively well absorbed[5].

The decomposition of Rifampicin has varied from 8.5 to 50% in the acidic environment of the stomach in the time range corresponding to the gastric residence time for the most dosage forms in humans. Gastric emptying time for single unit dosage forms may reach 6 hours. Rifampicin is known to undergo hydrolysis in acidic medium to the insoluble 3-formyl rifamycin SV . Isoniazide accelerates degradation of Rifampicin into this poorly absorbed derivative (3FRSV) in the acidic environment of the stomach through reversible formation of the isonicotitinyl hydrazone of 3-formyl rifamycin SV with Isoniazide.

In present research work, Rifampicin and Isoniazide bilayer tablets were formulated consisting of two layers such Rifampicin as immediate release layer and isoniazide as sustained release layer was prepared using super Disintegrants such as sodium starch glycolate and sustained release layer was prepared using HPMC such as (HPMCK 100M).

MATERIALS AND METHODS:

MATERIALS:

Rifampicin , isoniazide. Micro crystalline cellulose from FMC biopolymers ,india.HPMCK100, sodium starch glycolate from signet chemicals, India. Magnesium stearate from signet chemicals co. LTD, Mumbai. Starch and talc from loba chemie, Mumbai.

METHODS:

Direct compression method[15]:

1.Rifampicin and other excipient sifted through sieve number 40 and thoroughly mixed in a blunder approximately for 5 minutes.

2. Above mixture was lubricated with magnesium stearate and then sodium starch glycolate was used as super disintegrant.

FORMULATION FOR IMMEDIATE RELAESE RIFAMPICIN:

S.NO	INGREDIENTS	F1(mg)	F2(mg)	F3(mg)	F4(mg)
1	Rifampicin	400	400	400	400
2	Microcrystalline cellulose	60	60	60	60
3	Sodium starch glycolate	10	10	10	10
4	Starch	5	5	5	5
5	Magnesium stearate	2	2	2	2
6	Talc	2	2	2	2
7	Aerosil	2	2	2	2

Wet granulation method[15]:

1. Isoniazide , Microcrystalline cellulose, lactose, HPMCK100 were sifted through sieve number 40.

2. Starch was mixed in water. Granules were prepared and dried in tray drier at 65^0c. The granules were passed through mesh number 20.

3. Finally mixture was lubricated with talc and magnesium stearate.

FORMULATION FOR SUSTAINED RELEASE ISONIAZIDE:

S.NO	INGREDIENT	F1(mg)	F2(mg)	F3(mg)	F4(mg)
1	Isoniazide	300	300	300	300
2	HPMCK100	300	300	300	300
3	Microcrystalline cellulose	2	2	2	2
4	Magnesium stearate	3	3	3	3
5	Talc	3	3	3	3
6	Purified water	q.s	q.s	q.s	q.s

DISSOLUTION PARAMETERS:

MEDIUM :0.01M hydrochloric acid and phosphate buffer

P^H 6.8

APPARATUS :USP-type2 (paddle)

RPM :50

TEMPERATURE :37^0C

MEDIUM VOLUME :900ml

PROCEDURE:

The release of isoniazid from the IR layer was studied in 900ml of 0.01M HCL for first hour and isoniazid from sustained layer was studied in 900ml of phosphate buffer P^H 6.8 from 2 to 24 hours as dissolution medium using a USP dissolution paddle assembly at 50rpm and 37^0c.and aliquot (1ml) was withdrawn at specific time intervals and diluted with respective medium and drug content was determined by visible spectrophotometer at 270 nm for isoniazid. an equal volume of fresh dissolution medium replaced to maintain the sink condition.

EVALUATION :

PRE COMPRESSION PARAMETERS:

1. ANGLE OF REPOSE:

The flow property was determined by measuring the angle of repose. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal plane. Values of θ are rarely less than 20^0 ,values of up to 40^0 indicate reasonable flow potential. Above 50^0 however, the powder flows only with difficulty if at all.

$\theta = \tan^{-1}(h/r)$ where ,

h=height of the pile.

r=radius of the pile.

θ=angle of repose.

2. DETERMINATION OF BULK DENSITY AND TAPPED DENSITY:

A quantity of 20gm of the powder from each formula was introduced into a 100ml measuring cylinder. After the initial volume was observed ,the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density and the tapped density were calculated using the following formulas :

$$\text{Bulk density} = w/v_\theta$$

$$\text{Tapped density} = w/v_f$$

Where ,

W=weight of the powder.

V_0= initial volume

V_f = final volume

3. COMPRESIBILITY INDEX:

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is . A material having value of less than 18% is defined as free flowing material.

C1= compressibility index.

4. HAUSNER'S RATIO:

It indicates the flow properties of the powder and it is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's ratio} = (w/v_f)/(w/v_0)$$

Where,

w/v_f=tapped density

w/v_o=bulk density

thus,

Hausner's ratio= tapped density/ bulk density

S.NO	HAUSNER'S RATIO	PROPERTY
1	0-1.2	Free flowing
2	1.2-1.6	Cohesive powder

POST COMPRESSION PARAMETERS:

1.HARDNESS TEST:

Hardness test was carried out by using vankel (VK200) hardness tester. 3 tablets were used for each formulation in hardness test.

2.THICKNESS:

10 tablets were selected at random from individual formulations and thickness was measured by using vernier calipers scale, which permits accurate measurement.

3.FRIABILITY:

Friability is related to tablets ability to withstand both shock and abrasion without crumbling during manufacturing, packing, transport and consumer handling. Friability can be evaluated by means of friability test apparatus. Compressed tablets that loose less than 0.5%- 1.0% in weight are generally considered acceptable.

METHOD:

Upto 10 tablets were transferred into friabilator and subjected to 100 revolutions in 4 mints . Dedusted tablets were re weighed (final weight).Friability was calculated as below formula:

% Friability= (initial wt-final wt)/(initial weight)* 100

4. WEIGHT VARIATION:

20 tablets are selected at random and average weight was determined not more than 2 of the individual weights should deviate from the average weight by more than the % deviation shown in the table and none should deviates by more than twice the %.USP official limits of % deviation of tablet were presented in table

S.NO	AVG WEIGHT OF TABLETS	MAXIMUM % DIFFERENCE ALLOWED
1	130 0r less	10
2	130-324	7.5
3	More than 324	5.0

% maximum positive deviation =(wh-A/A)×100

% minimum negative deviation=(A-wL/A)×100

Where,

wH=highest weight in mg

wL=lowest weight in mg

A=average weight of tablet in mg.

5. *IN-VITRO* DRUG RELEASE STUDIES:

The in-vitro dissolution characteristics of Rifampicin and Isoniazid bilayer tablets are shown Table No.3 Based on the in-vitro release profile of drug formulations of F1 to F4, the formulation F3 showed better drug release, which was achieved by increasing the polymer concentration HPMC K-100M which release the drug in a controlled rate at regular time intervals in appropriate concentrations as per the limits. Hence formulation F3 was selected for further stability studies.

LIST OF TABLES :

PRECOMPRESSION (MEAN±SD) TABLE: 1

S. NO	FORMULAT -IONS	ANGLE OF REPOSE (in ^{0})	BULK DENSITY (gm/cm^3)	TAPPED DENSITY (gm/cm^3):	HASUNER' S RATIO	COMPRESS -ABILITY INDEX
1	F1	29.24± 0.267	0.323± 0.002	0.334± 0.0015	1.16± 0.015	13.73± 1.149
2	F2	28.11± 0.555	0.342± 0.014	0.313± 0.03	1.19± 0.028	15.77± 2.025
3	F3	27.77± 0.608	0.336± 0.0025	0.325± 0.003	1.17± 0.012	14.4± 1.945

POSTCOMPRESSION (MEAN±SD) TABLE: 2

S. NO	FORMULATI -ON	HARDNESS (k_g/cm^2)	FRIABILITY (%)	WEIGHT VARIATI -ON TEST(mg)	DISINTEG -RATION TIME(IR) (in sec)	DRUG CONTENT FOR (INH) (%)	DRUG CONTENT FOR (RIF) (%)
1	F1	19.47± 0.1247	0.05± 0.0048	1051± 0.8165	66± 1.633	98.98± 0.5258	98.14± 0.3756
2	F2	19.43± 0.33	0.07± 0.0012	1053.33± 1.2472	62.67± 0.9428	99.27± 0.2722	99.14± 0.2868
3	F3	19.4± 0.1633	0.05± 0.0048	1049.33± 2.0548	54± 1.4142	99.46± 0.2610	100.07± 0.2868

STANDARD CURVE TABLE FOR RIFAMPICIN AND ISONIAZID: TABLE:3

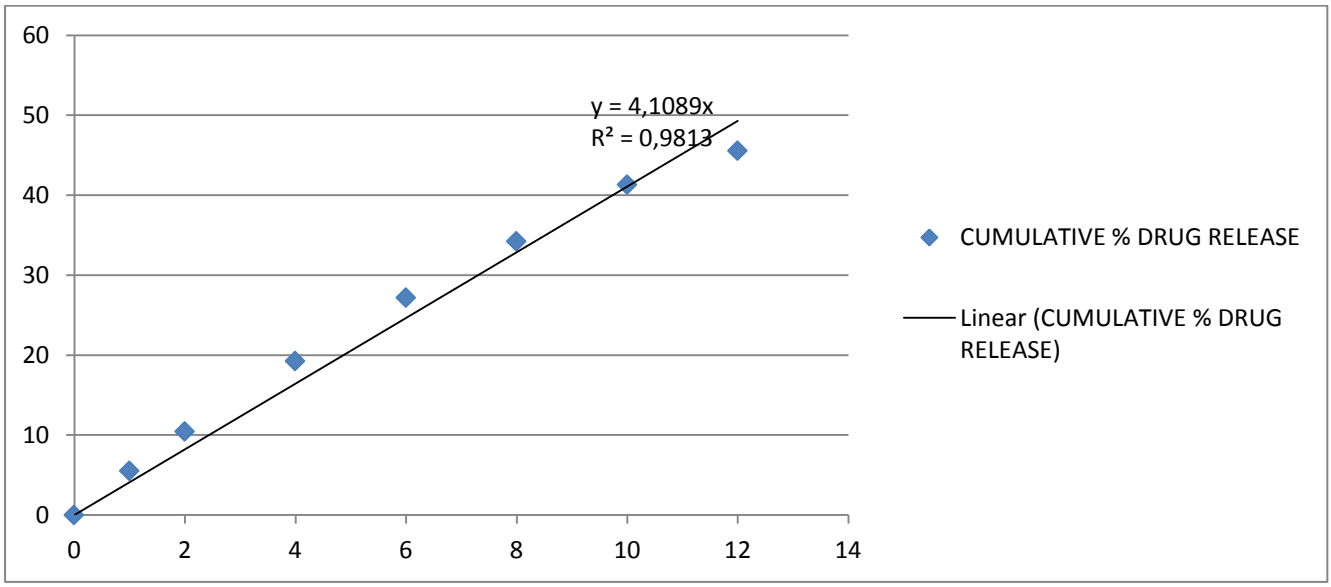
S.NO	CONCENTRATION	ABSORBANCE	
		RIFAMPICIN	ISONIAZID
1	0	0	0
2	5	0.092	0.11
3	10	0.155	0.192
4	15	0.202	0.281
5	20	0.264	0.370
6	25	0.316	0.450
7	30	0.348	0.547
8	35	0.420	0.634

% DRUG RELEASE FOR F3 : TABLE :4

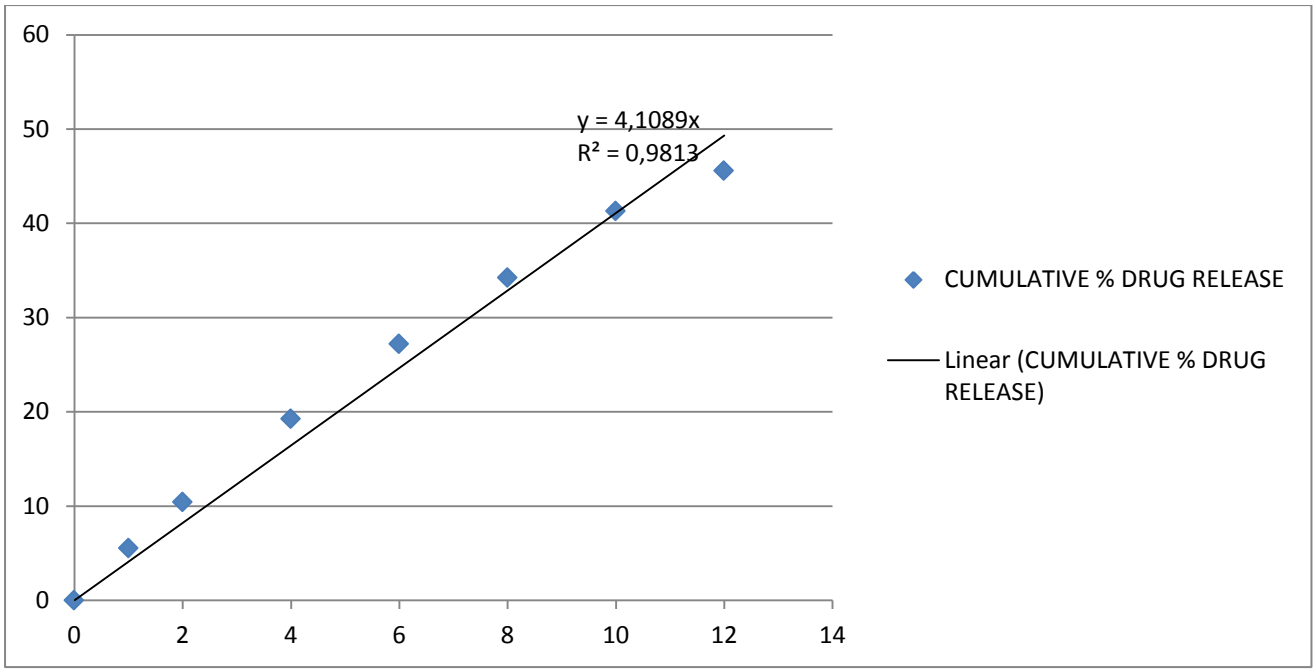
Time	Absorbance	Con In Mcg/Ml	Amount Release In Mg/Ml	Cumulative Amount Released In 900ml In Mg	Cumulative % Drug Release	Cumulative %Drug Remaining	Log Cumu %Drug Remaining	Square Root Of Time	Log Time
0	0	0	0	0	0	100.00	2.0000	0	-
1	0.006	0.5028	0.0010	0.5531	5.53	94.47	1.9753	1.0000	0.
2	0.011	0.9435	0.0019	1.0429	10.43	89.57	1.9522	1.4142	0.3010
4	0.02	1.7368	0.0035	1.9249	19.25	80.75	1.9071	2.0000	0.6021
6	0.028	2.4419	0.0049	2.7179	27.18	72.82	1.8623	2.4495	0.7782
8	0.035	3.0589	0.0061	3.4211	34.21	65.79	1.8182	2.8284	0.9031
10	0.042	3.6759	0.0074	4.1303	41.30	58.70	1.7686	3.1623	1.0000
12	0.046	4.0285	0.0081	4.5549	45.55	54.45	1.7360	3.4641	1.0792
24	0.09	5.6338	0.0113	6.3610	63.61	36.39	1.5610	4.8990	1.3802
48	0.115	7.8374	0.0157	8.8413	88.41	11.59	1.0640	6.9282	1.6812

LIST OF GRAPHS:

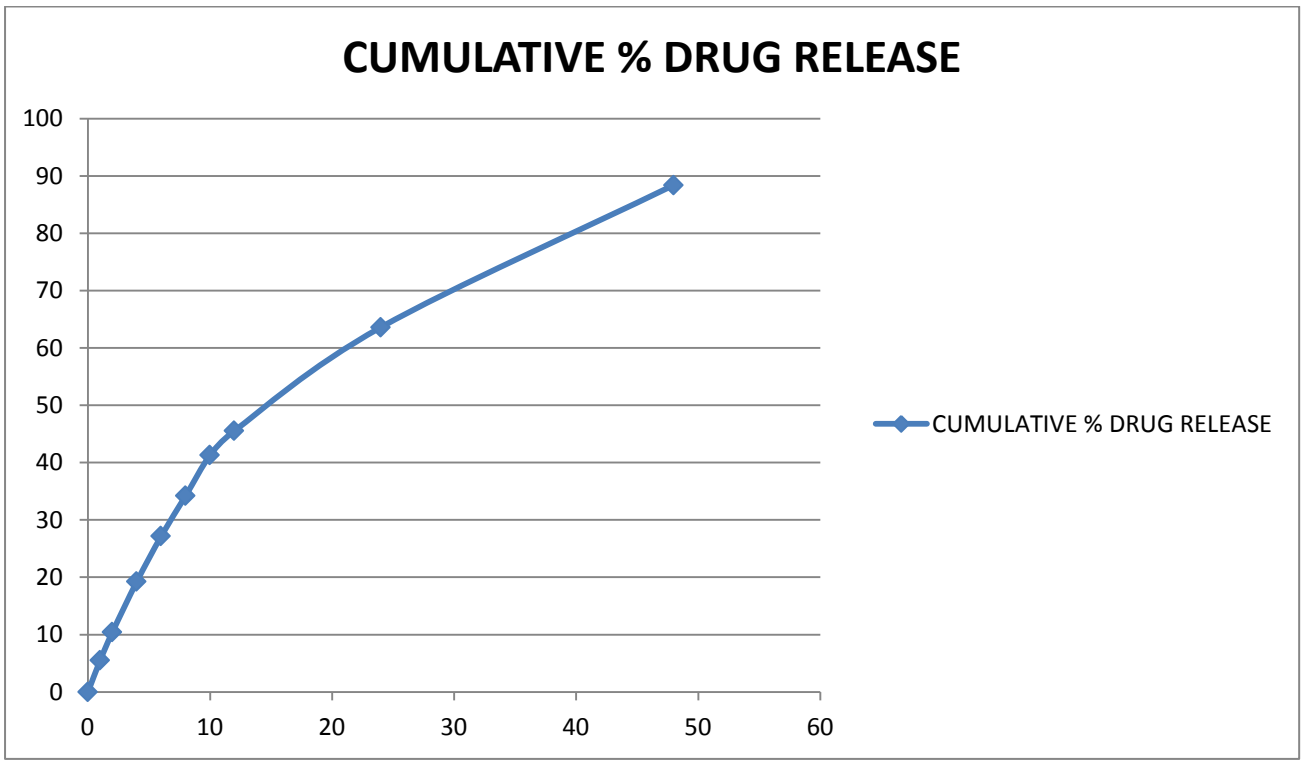
STANDARD GRAPH FOR RIFAMPICIN: GRAPH 1



STANDARD GRAPH FOR ISONIAZID: GRAPH 2



IN-VITRO **DRUG RELEASE FOR FORMULATION F3 : GRAPH 3**



CONCLUSION:

Rifampicin and isoniazid employed as first line anti tubercular drug .It is reported that while giving combination therapy with isoniazid degradation of rifampicin has been increased. To reduce the degradation of rifampicin we formulated bilayer tablets containing rifampicin as immediate release and isoniazid as sustained release with different concentration of sodium starch glycolate and HPMC. The result showed that F3 has better release profile compared to other formulation. Hence it was concluded that this bilayer tablet will reduce the degradation of rifampicin in the presence of INH administrated orally. The pre compression and post compressions showed that all formulations has complies with the standard value which is suitable for the preparation of tablets by suitable method. The in-vitro disintegration and dissolution shown that F3 has better release profile compared with other formulation.

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