ISSN No:-2456-2165

Design and Characterization of Bilayer Tablet of Rifampicin and Isoniazid for Tuberculosis Therapy

Dr. Subashini Rajaram[1], Dr. Senthil Rajan[2], B. Jamuna[3]*, V. Divya[4], P. Elango[5], M. Farheen Kausar[6], Gogineni Chandan[7]
Department of Pharmaceutics, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode

Abstract:- The present study aim was to formulate and evaluate the bilayer tablets containing Rifampicin immediate release layer (IR) and isoniazid in the sustained release (SR) layer in the way to develop a single tablet containing two different layers of drugs as widely used by physician and have better patient compliance. The SR layer of Isoniazid was developed by the method of wet granulation and using the grade of HPMCK100m, and other excipients like lactose, magnesium stearate, microcrystalline cellulose & talc. The IR layer of Rifampicin was developed by the method of direct compression. The powders are characterized by pre formulation properties and tablets are characterized by post formulation properties. The in-vitro study of Rifampicin and Isoniazid using USP(type 2) dissolution apparatus. The release rate studied for 45 mins by using 0.1M HCL and phosphate buffer P^H 6.8 for 2hrs absorbed by UV spectrophotometry. Rifampicin release rate from the formulations was more than 80% at 45 min by adding HPMCK100m. Total three batches of each drug have been manufactured and developed stable formulation, the stability studies was complied as per International Conference of Harmonization guidelines.

Keywords:- *HPMC, IR,SR,ICH Guideline, UV Method , USP.*

I. INTRODUCTION

On present days developed and developing countries improve the combination therapy for long term use for various diseases and disorders such as tuberculosis, cancer, HIV/AIDS. Combination therapy have most advantages when compare to mono therapy to reduce the dose dependent toxicity, a less dosage combination of 2 different compound decreases the dose dependent side effect , when the addition of one or two compound in one formulation may counter interaction with each another, using less dosage of 2 different compound reducing clinical trial and therapeutic action that obtain maximum dose of individual compounds in the combination tablet[1].

The aim in developing sustained or controlled delivery systems is to reduce the frequency of dosing and increases the effectiveness of the drug by specification at the site of action, and to providing the uniform drug delivery. If in design novel drug delivery system, Two prerequisites would be required. First, it would be a single dose enough for the treatment for weeks or months for tuberculosis therapy and also various diseases. Second one is deliver the Active pharmaceutical ingredient directly into specific site action , And minimize the side effect of formulation[2].

Tuberculosis is a bacterial infection, is a now a days leading killer of the younger 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 guided by WHO (world health organization) treated for tuberculosis and drug resistance cases require bi or multi drug therapy we needed.

- The first phase of Rifampicin, Isoniazide, Pyrazinamide, Ethambutol daily for 2 months.
- The continous phase of Rifampicin, Isoniazide for a another 4 or 6 months for daily or 3 times / week to be administered by the patient for treatment.

Therefore the present work is aimed to develop bilayer tablets having Rifampicin (IM) and Isoniazide (SR) 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.

BCS (Permeability) studies is expressed that Rifampicin is well absorption in the stomach because of its solubility, the results is maximum between pH 1-2, although expressed solubility in the GIT environment is comparatively well absorbed[5] in the stomach.

The degradation of Rifampicin is varies from 8.5 to 50% in the acidic medium of the stomach in the time (t) range corresponding to the gastric residence time (GRT) most of the dosage forms in humans. GET(Gastric emptying

ISSN No:-2456-2165

time) for single unit dosage form release rate in 6 hours. Rifampicin undergoes into hydrolysis in acidic medium and develop a insoluble form of 3-formyl rifamycin SV. Isoniazide short term degradation of Rifampicin into this insoluble derivative (3FRSV) in acidic medium in GIT through returned form of isonicotitinyl hydrazone of 3-formyl rifamycin SV with Isoniazide.

In present research work, Rifampicin and Isoniazide bilayer tablets were formulation consist of two layers such a Rifampicin as (IM) layer and isoniazide as (SR) layer was developed by using super Disintegrants such as sodium starch glycolate and SR layer was developed by using HPMC such as (HPMCK 100M).

II. MATERIALS AND METHODS:

A. 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.

B. 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 SSG (sodium starch glycolate) used as a super disintegrant.

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(MgSt)	2	2	2	2
6	Talc	2	2	2	2
7	Aerosil	2	2	2	2

Table 1:- Formulation for Immediate Release Rifampicin:

➢ *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 drying can occur by tray drier at 65^0c. After that granules are passed through the sieve number #20.
3. Finally the granules was lubricated done by talc and magnesium stearate.

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	water	Q.S	Q.S	Q.S	Q.S

Table 2:- Formulation For Sustained Release Isoniazide

➢ *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 0.1M HCL for first hour and isoniazid from sustained layer was studied in 900ml of P^H 6.8 phosphate buffer for 2 to 24 hours as dissolution medium using a USP dissolution apparatus (paddle type) assembly at 50 rpm and 37^0c and aliquot (1ml) sample withdrawn at specific time intervals and dilute with respective medium and drug release was determined by UV spectrophotometer at 270 nm for isoniazid. And maintain the sink condition.

III. EVALUATION

A. Pre Formulation Parameters:

➢ *Determined the Angle of Repose:*

Determined the flow properties by measured the angle of repose of powder. 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.

➢ *Characterization of Bulk Density and Tapped Density:*

Weigh accurately the quantity of 20gm powder from the each formulation is poured in a 100ml of cylinder(measuring). And note the first intial volume, after that cylinder (measuring) allowed to tap onto a flat surface area in the 2.5cm height at regular 2 second intervals. The tapping should continue until the changes not occur in the final volume of powder.

Bulk density was calculated by using the following formula :

Bulk density = w/v_0

Tapped density was calculated by using the following formula :
Tapped density = w/v_f

Where,
W = Weight of the powder.
V_0 = Initial volume.
V_f = Final volume.

➢ *COMPRESIBILITY INDEX (IDX):*

Compressibility indx is defined as a measured the bulk and tapped densities. In this theory, the less compressible material and the more flowable on its .The material should be less than 18% value is called as free flowing material.

C1= compressibility index.

➢ *Determine The Hausner's Ratio:*

Determine the flow properties of the powder and measured by its ratio of tapped density and the bulk density.

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

Table 3

B. Post Compression Parameters:

➢ *Hardness Test:*

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

➢ *Thickness:*

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

➢ *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 is accepted standard value.

Method:

Upto 10 tablets are 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

➢ *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 or Less	10
2	130 - 324	7.5
3	More Than 324	5.0

Table 4

% maximum + deviation =(wH-A/A)×100
% minimum - deviation=(A-wL/A)×100

Where,
W H=highest wt in mg
w L=lowest wt in mg
A = Average wt of the tablet in mg.

➢ *In-Vitro STUDIES:*

The in-vitro studies for Rifampicin and Isoniazid bilayer tablets are seen in Table No.7 Based on in-vitro dissolution profile of F1 to F3, the maximum drug release showed by formulation F3,by increasing the polymer concentration HPMC K-100M the release of drug in a controlled manner at a regular time intervals as per the specification. The F3 was stored for further studies.

IV. LIST OF TABLES

S. NO	FORMULATIONS	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

Table 5:- Precompression (Mean ± Sd)

S. NO	FORMULATION	HARDNESS (k_g/cm^2)	FRIABILITY (%)	WEIGHT VARIATION TEST(mg)	DISINTEGRATION TIME(IR) (in sec)	DRUG CONTENTFOR (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

Table 6:- Postcompression (Mean ± Sd)

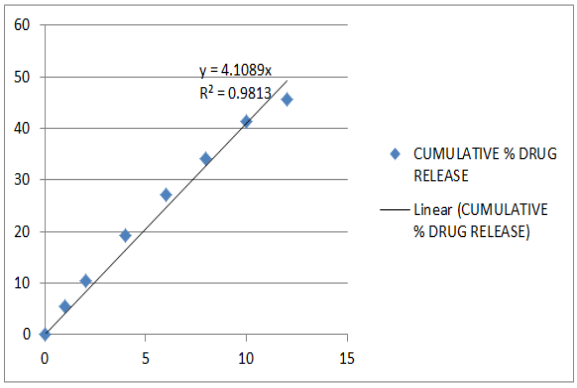
S. NO	CONCENTRATION	ABSORBANCE	
		RIFAMPICIN	ISONIAZID
1	0	0	0
2	5	0.092	0.11
3	10	0.155	0.192
4	15	0.202	0.281
5	20	0.264	0.370
6	25	0.316	0.450
7	30	0.348	0.547
8	35	0.420	0.634

Table 7:- Standard Curve Table for Rifampicin and Isoniazid

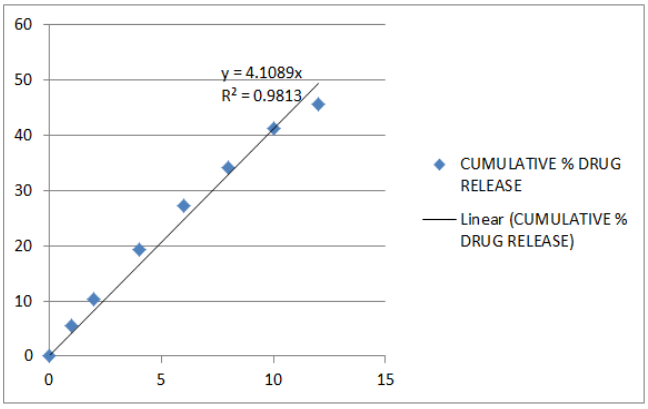
Time	Absorbance	Con In Mcg/Ml	Amount Release In Mg/Ml	Cumulative Amount Released In 900ml In Mg	Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumu %Drug Remaining	Square Root of Time	Log Time	Log Cumulative % Drug Release
0	0	0	0	0	0	100.00	2.0000	0	-	-
1	0.006	0.5028	0.0010	0.5531	5.53	94.47	1.9753	1.0000	0.	0.7428
2	0.011	0.9435	0.0019	1.0429	10.43	89.57	1.9522	1.4142	0.3010	1.0182
4	0.02	1.7368	0.0035	1.9249	19.25	80.75	1.9071	2.0000	0.6021	1.2844
6	0.028	2.4419	0.0049	2.7179	27.18	72.82	1.8623	2.4495	0.7782	1.4342
8	0.035	3.0589	0.0061	3.4211	34.21	65.79	1.8182	2.8284	0.9031	1.5342
10	0.042	3.6759	0.0074	4.1303	41.30	58.70	1.7686	3.1623	1.0000	1.6160
12	0.046	4.0285	0.0081	4.5549	45.55	54.45	1.7360	3.4641	1.0792	1.6585
24	0.09	5.6338	0.0113	6.3610	63.61	36.39	1.5610	4.8990	1.3802	1.8035
48	0.115	7.8374	0.0157	8.8413	88.41	11.59	1.0640	6.9282	1.6812	1.9465

Table 8:- % Drug Release For F3 :

V. LIST OF GRAPHS:

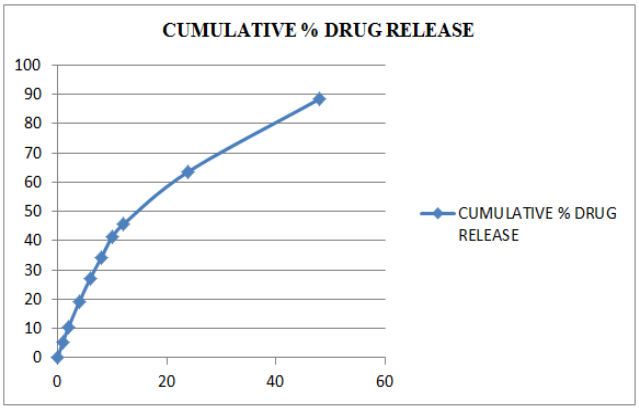


Graph 1:- Standard Graph for Rifampicin



Graph 2:- Standard Graph for Isoniazid:

ISSN No:-2456-2165



GRAPH 3:- In-vitro Drug Release for Formulation F3

VI. 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 having rifampicin (IR) and isoniazid (SR) with different concentration of sodium starch glycolate and HPMC. The result was shown by F3 has better drug release profile when compared to other formulation. Hence it was concluded that this bilayer tablet will reduce the biodegradation of rifampicin by presenting the INH when 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.

REFERENCES

[1]. R.Amrutkar Jitendra, G.Kalaskar Mohan. G.Shrivastav varsha., P.G.Yeole., formulation of Bilayer tablet of Rifampicin and Isoniazid: A smart (novel) approaches in the treatment of tuberculosis.

[2]. Joseph R.Robinson, Gwen M.Jantzan. Sustained and controlled release drug delivery systems In:Editors,GilbertS.banker.Modern pharmaceutics. 4th Edition Revised and expanded. Marcel Dekker Inc; Newyork.USA.2008 pg.500-530.

[3]. World Health Organization. Global tuberculosis control: surveillaplanning, financing, WHO Report 2003 (WHO/CDS/TB/2003.316).Geneva: WHO, 2003nce,

[4]. R. Nagaraju, Rajesh Kaza., Formulation and evaluation of Bilayer sustained release tablets of salbutamol and theophylline., International journal of pharmaceutical sciences and Nanotechnology., 2009,2(3),638-646.

[5]. Sean C Sweetman., Martindale The complete Drug Reference., 36th Ed.2009, 433.

[6]. Enarson DA, Rieder HL, Arnadottir T, Trébucq A. Management of tuberculosis: a guide for low-income countries, 5th edn. Paris: International Union Against Tuberculosis and Lung Disease, 2000:

[7]. Fox W. Compliance of patients and physicians: experience and lessons from tuberculosis I. *BMJ* 1993; **287:** 33–35.

[8]. Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis' *Engl J Med* 1994: **334:** 1179–84.

[9]. http://futuretrendinpharmatech.blogspot.com.

[10]. Patel Mehul,Ganesh nanjan Sockan,kavitha, Tamizh Mani., Challenges in the formulation of Bilayerd tablets: a review., *International journal of Pharma Research and development.*, 2010,2(10),30-42.

[11]. Chein YW.NOVEL DRUG DELIVERY SYSTEMS .Marcel Dekker Inc.2nd Ed.1992:139-40.

[12]. Leath E,Appel DT, Friesen JE,Byers MD, Crew BC,Hancock SJ,Schadtle. Immediate release dosage forms containing solid drug distribution. United States Patent No.424465; 2002.

[13]. Das, N.G., & Das S.K.,2003. Controlled –release of oral Dosage Forms. Formulation, Fill&finish:10-16.

[14]. Collet, J.,& Moreton,C.,2002.Modified-release per oral dosage forms.In:Aulton, M.E.,(Ed).2002. Pharmaceutics; The science of dosage Form Design.2nd Edition. Churchill Livingstone :United Kingdom :289-305.

[15]. Micael D.Tousey., The Granulation Process 101, Basic Technologies for Tablet Making.,Available from pharmtech.com.

[16]. Raymond C Rowe, Paul J Sheskey,Marian E Quinn., Handbook of pharmaceutical Excipients., 6th Edition ., 326-329.

[17]. Sodium starch glycolate, Available from URL:http://www.chemblink.com.

[18]. Artur H.Kibbe, American pharmaceutical association and pharmaceutical society of Great Britain. Handbook of pharmaceutical excipients,3rd edition.1986,pg.no.525-530.

[19]. Arthur H.Kibbe. Sodium stach glycolate In: Arthur H.Kibbe.editors. Handbook of pharmaceutical Excipients..Pharmaceutical press.London. 3rd Ed .pg.501-504.

[20]. Sodium starch glycolate In: Arthur H.Kibbe.editors.Handbook of pharmaceutical Excipients . Pharmaceutical press.London. 3rd Ed.pg.555-557.

[21]. M. Silverstein Robert, X.webster Francis. IR Specrometry. In: Editors,M.Silverstein Robert. Spectrometric Identification of organic compounds .John Wiley and Sons .Inc.Newyork. 6th Ed .pg.71-143.

[22]. Keith Marshall .Compression and consolidation of powdered solids.In :Herbet A. Leiberman,Joseph L.Kanig,Leon Lachman Editors. The theory and practice of Industrial Pharmacy .3rd Ed. (indin) , Varghese publishing house ;Mumbai.pg.66-99.

[23]. C.V.S.Subrahmanayam. Micromeritics.In:C.V.S. Subrahmanayam. Editors.Textbook of physical pharmaceutics .2nd Ed.Vallabh Prakashan.Delhi.2000.pg.no.180-234.