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FORMULATION AND EVALUATION OF FIXED DOSE COMBINATION PRODUCTS OF ANTITUBERCULAR DRUG

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ABSTRACT

Objective of the present study is to formulate and evaluate fixed dose combination tablets of Rifampicin and Isoniazid. The granules of Rifampicin and Isoniazid were prepared separately by wet granulation, then lubricated blend was compressed using tablet compression machine by setting the machine speed in the range 12- 28 RPM with desired processing parameters such as average weight, uniformity of weight, thickness, hardness & friability. These tablets were evaluated for the various physical parameters like appearance, weight variation, hardness, friability and disintegration. Coating was done in Ganscoater coating pan in two lots. Dissolution studies FDC tablets were performed along with uncoated and film coated tablets separately. The cumulative percentage drug release for coated tablet was found to be around 96%. From in vitro studies it was concluded that the prepared tablet gives more satisfactory results and patient compliance.

KEY WORDS: Rifampicin, Isoniazid, Film coating, fixed dose combination products, Ganscoater, tuberculosis.

INTRODUCTION

The design strategy focussed on overcoming the inherent stability problems encountered with this 2-FDC tablet dosage form. According to literature Rifampicin is not only prone to hydrolysis and oxidation, but it can also react (indirectly though acid degradation or directly) with isoniazid to form a hydrazone. The manufacture involves two separate wet granulation processes, one for Rifampicin and the other for Isoniazid the dried granules are blended with Rifampicin, which is introduced extra granularly, and compressed. Finally the tablets are

film-coated.[1] Tuberculosis was for centuries a major killer disease. With the development of the first line drugs, it came to be regarded as an easily curable condition. This is no longer easily curable as the bacteria Mycobacterium tuberculosis which causes it has come back to haunt us. Multidrug-resistant strains are now common and recent evidence suggests that strains with increased virulence have emerged. [2] One of the main reasons for the development of this resistance is the mono drug therapy. This may be due to the drug-drug interactions as the therapy includes combination of various fixed dose of drugs leading to poor bioavailability. [3] One such commonly reported interaction is between Rifampicin and Isoniazid, the two extensively used drugs in the treatment of Tuberculosis leading to the poor stability and bioavailability of Rifampicin [4]. The present study deals with formulation and evaluation of the dosage forms by film coating. [5]

MATERIALS AND METHODS

TABLE 1: LIST OF MATERIALS

Sr .no.	Materials	Vendor
1	Rifampicin	Amsal chem. Pvt ltd Ankleshwar
2	Isoniazid	Lupin limited Tarapur
3	Microcrystalline cellulose	RANQ Remidies limited
4	Pregelatinized starch(starch 1500)	Colorcon Indiaapolice pvt. Ltd
5	Crospovidonpolypsdon	ISP Chemicals
6	Ascorbic acid	DSM nutritional products, Germany

TABLE 2: LIST OF EQUIPMENTS

SR.NO.	EQUIPMENT	SUPPLIER/MANUFACTURER
1	Tablet compression machine	Sejong
2	Coating machine	Gansons
3	Tap Density Tester	Electro lab (ETD -1020), Mumbai, India
4	Metal Detection Unit- Metal Trap	Electro lab (ETD -1020), Mumbai, India
5	Vernier Calliper Scale	Mitutoyo, Aurora, USA
6	Tablet Hardness Tester	Manchester, USA
7	Tablet Friability Apparatus	Electro lab (EF-1W), Mumbai, India
8	Tablet Disintegration Test Apparatus	Electro lab (ED-2AL), Mumbai, India
9	Tablet Dissolution Apparatus	Electro lab, Mumbai, India
10	UV- visible spectrophotometer	Shimadzu 1800
11	HPLC	Shimadzu
12	Weighing balance with LC P45 printer	Sartorius

METHODOLOGY

PREPARATION OF THE FORMULATIONS

The manufacture involves two separate wet granulation processes, one for Rifampicin and the other for Isoniazid. The dried granules are blended with Rifampicin, which is introduced extra-granularly, and then the wet granules were dried by initial air dry procedure in FBD. The granules were evaluated for the physical parameters like bulk density, tap density, compressibility index, Hausner's ration, particle size distribution. The lubricated granules obtained by wet granulation were blended in blender and then compressed in compression machine with respective weight of tablet required. Film coating was carried out in coating machine. The prepared Rifampicin and Isoniazid tablets were evaluated for the physical parameters like hardness, weight variation, friability, disintegration and dissolution.

TABLE 3: ISONIAZID PART

SR.NO.	INGREDIENTS	QUANTITY (gm) BATCH	FUNCTION
1	Isoniazid	9.0000	Active ingredient
2	Microcrystalline Cellulose	2.6400	Diluent / Disintegrant
3	Pregelatinized Starch	0.3600	Disintegrant
4	Purified Water	2.2000	Solvent, Granulation Aid

TABLE 4: RIFAMPICIN PART

SR. NO.	INGREDIENTS	QUANTITY (gm)	FUNCTION
1	Rifampicin	9.1800	Active ingredient
2	Microcrystalline Cellulose	2.3748	Diluent / Disintegrant
3	Crospovidone Polyplasdone	0.6000	Disintegrant
4	Pregelatinized Starch (Starch 1500)	1.3452	Binder
5	Pregelatinized Starch	0.6000	Binder
6	Ascorbic Acid	0.1800	Preservative
7	Purified Water	6.7500	Solvent, Granulation aid

TABLE 5: LUBRICATION PART

SR. NO.	INGREDIENTS	QUANTITY (gm)	FUNCTION
1	Microcrystalline Cellulose	0.4080	Diluent
2	Coloidal Silicon Dioxide	0.3240	Glidant
3	Crospovidone (Polyplasdone)	1.4760	Disintegrant
4	Magnesium Stearate	0.4320	Lubricant

Evaluation Of Physical Characteristics Of Lubricated Granules

1. Bulk density

Granules of approximately 50 gm is weighed and poured in to 100ml glass measuring cylinder. The initial volume occupied (in ml) by material is noted down.

2. Tapped density

Granules of approximately 50 gm is weighed and poured in to 100 ml glass measuring cylinder. The initial volume occupied (in ml) by material is noted down, and it is tapped for 500,750,1250 taps in tap density apparatus, the volume occupied by material after tapping was noted down, the tap density after 500, 750 and 1250

3. Compressibility index

Granules of approximately 50 gm is weighed and poured in to 100 ml glass measuring cylinder. The initial volume occupied (in ml) by material is noted down, and it is tapped for 500 taps in tap density apparatus, the volume occupied by material after tapping was noted down.

4. Hausner's ration

Granules of approximately 50 gm is weighed and poured in to 100 ml glass measuring cylinder. The initial volume occupied (in ml) by material is noted down, and it is tapped for 500 taps in tap density apparatus, the volume occupied by material after tapping was noted down.

TABLE 6: PHYSICAL CHARACTERISTICS OF LUBRICATED GRANULES

SR. NO.	PARAMETERS	BATCH NO.		
		GA-01	GA-2	GA-03
1	Description	Brick red colour granular powder	Brick red colour granular powder	Brick red colour granular powder
2	Bulk density gm/ml	0.569	0.520	0.566
3	Tapped density gm/ml (500 Taps)	0.709	0.708	0.700
4	Tapped density gm/ml (750 Taps)	0.739	0.737	0.730
5	Tapped density gm/ml (1250Taps)	0.739	0.737	0.730
6	Compressibility Index (%) (considering TD - 500 Taps)	19.670	26.090	19.350
7	Hausner Ratio (considering TD - 500 Taps)	1.244	1.350	1.240

8	Particle Size Distribution	%Cumulative Retention	%Cumulative Retention	%Cumulative Retention
	Over 20 #	0.99	0.97	0.96
	Over 40 #	11.16	12.09	12.07
	Over 60 #	28.02	29.27	29.30
	Over 80 #	34.15	35.42	35.45
	Over 100 #	46.05	47.43	47.45
	Below 100 #	51.41	50.24	50.63

FINAL PRODUCT TESING

1. Description

Examined 20 tablets for colour, chipping, peeling of coating, coating quality of cracks under the visible light.

Observations

Brick red coloured, capsule shaped biconvex film coated tablets, with break line on one side and plain on other side.

2. Average weight and Uniformity of weight

Randomly 20 tablets was selected, weighed 20 tablet individually and the average weight was calculated.

3. Hardness: The hardness of the test was carried out by using a MONSANTO hardness tester during different time intervals of compression.

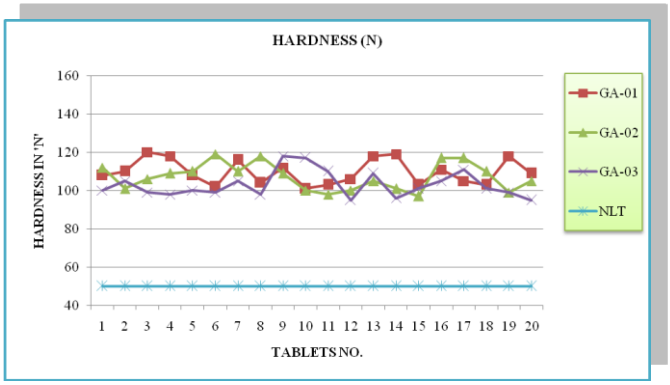


Figure 1: Graphical Representation Of Hardness

4. Thickness: Dial gauge vernier scale was used to determine thickness of each tablet, the tablet placed with its width in the jaw of the vernier scale, noted down the reading displayed on the liquid crystal display screen of the vernier.

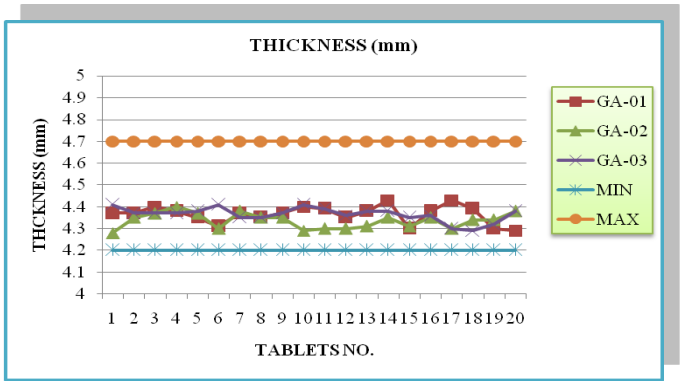


Figure 2: Graphical Representation Of Thickness

5. Friability: 20 tablets were accurately weighed and transferred to friability test apparatus, then rotated for 100 rotations, and then tablets were removed and reweighed after dedusting. The friability was determined by using following formula.

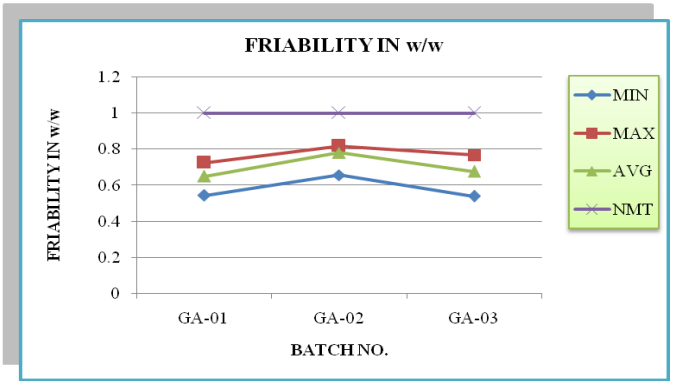


Figure 3: Graphical Representation Of Friability

6. Weight variation

Weight of tablets were determined the percent deviation of each tablet weight against the average weight of tablet was calculated. The test requirement are met, if not more than individual weights deviates from average weight by more than 5% and none deviates more than 10%.

7. Disintegration Time

The temperature of bath liquid and water was ensured that (37 ^{0}C ± 1 ^{0}C) 6 tablets were introduced in to the basket rack assembly of disintegration test apparatus and disk was added to each tube. Disintegration times of the six tablets were noted.

TABLE 7: EVALUATION FINAL PRODUCT

SR. NO.	PARAMETERS	BATCH		
		GA-01	GA-02	GA-03
1	Description	Brick red colour granular powder	Brick red colour granular powder	Brick red colour granular powder
2	Average weight (gm)	0.3598	0.3597	0.3615
3	Uniformity weight (gm)	0.3605	0.3605	0.3615
3	Hardness (N)	94	93	94
4	Thickness (mm)	4.2	4.3	4.2
5	Friability (% w/w)	0.44	0.65	0.53
6	Disintegration time (min: sec)	2.05	2.18	2.48

Evaluation

All the physical compression parameters for three batches were within limit and found satisfactory.

8. Dissolution test

Required numbers of tablets according to IP [8] were added into the Dissolution Test apparatus (USP I) at 50 RPM and the absorbance of standard and test preparation measured at 475 nm against dissolution medium as a blank. % Rifampicin and % Isoniazid dissolved was analysed in 0.1N Hydrochloric acid.

TABLE 8: DISSOLUTION DURING COMPRESSION OF RIFA

% Dissolution	BATCH		
	GA-01	GA-02	GA-03
RIFA	93	94	93
INH	91	89	90

Evaluation

% dissolution of RIFA at initial, middle and end stage of compression of three validation batches was found in the range 93 -100 %, which was within the acceptance criteria.

HPLC GRAPH OF DISSO 01 RIFA

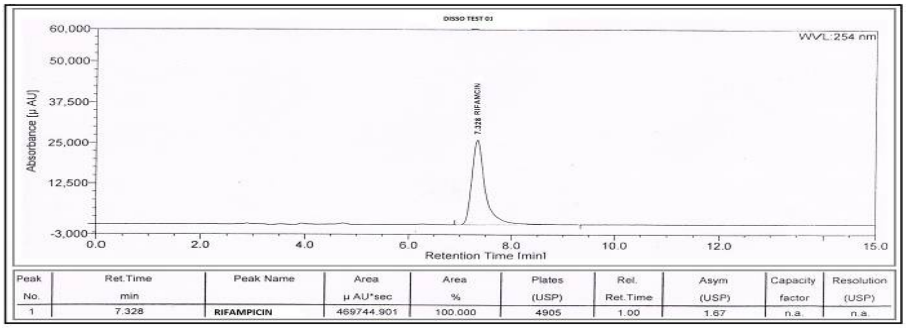
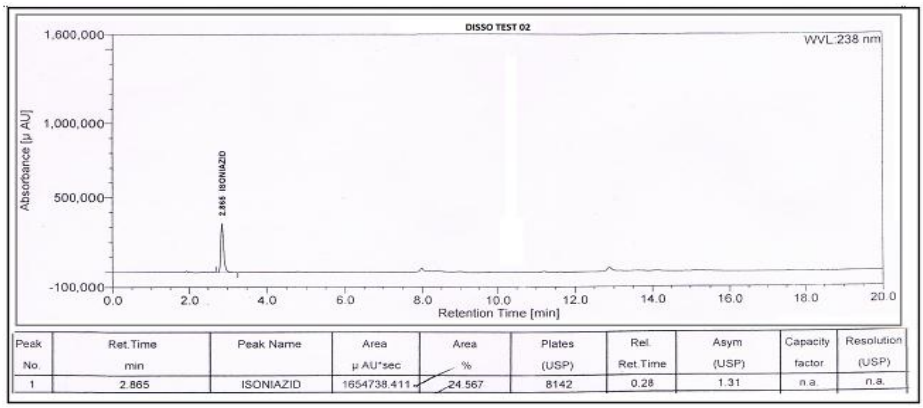


Figure 4: hplc graph disso 01 rifa Hplc graph of disso 02 inh



Peak No.	Ret.Time min	Peak Name	Area µ AU*sec	Area %	Plates (USP)	Rel. Ret.Time	Asym (USP)	Capacity factor	Resolution (USP)
1	2.865	ISONIAZID	1654738.411	24.567	8142	0.28	1.31	n.a.	n.a.

Figure 5: Hplc Graph Disso 02 Inh

9. ASSAY OF TABLETS

Procedure

Standard and test solutions were filtered through 0.45µ membrane filter. 20µ litre of blank and standard solution 1 in single injection, 5 replicate injections of standard solution 2 and test solution in duplicate injection injected into chromatograph, recorded the chromatogram and measured peak response as mentioned in below table.

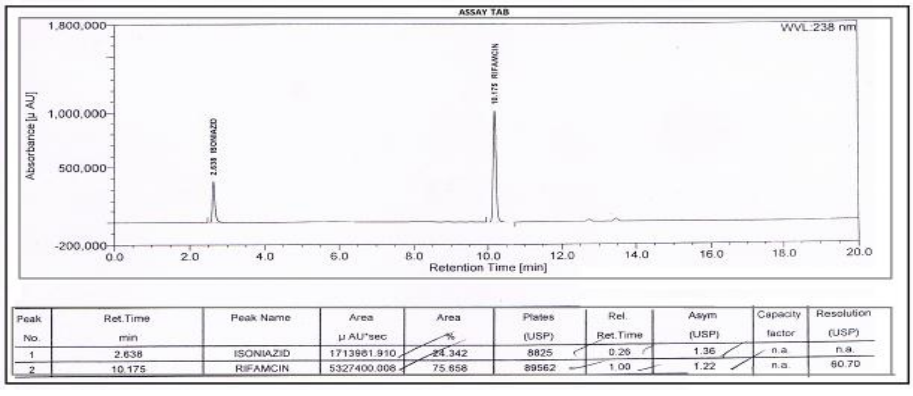
TABLE 9 ASSAY OF COMPRESSED TABLETS

LIMIT		BATCH NO.	Assay (%)
RIFA	142.50– 165.00 mg (95.0 -110.0%)	**GA-01**	100.0
		GA-02	97.2
		GA-03	97.9
INH	71.25 – 78.75 mg (95.0–105.0%)	**GA-01**	98.1
		GA-02	98.8
		GA-03	99.5

Evaluation

Assay of RIFA and INH at of compression was found within the limits.

Hplc Graph Of Assay



Peak No.	Ret.Time min	Peak Name	Area µ AU*sec	Area %	Plates (USP)	Rel. Ret.Time	Asym (USP)	Capacity factor	Resolution (USP)
1	2.638	ISONIAZID	1713961.910	24.342	8825	0.26	1.36	n.a.	n.a.
2	10.175	RIFAMCIN	5327400.008	75.658	89562	1.00	1.22	n.a.	60.70

Figure 6: Hplc Graph Assay

RESULT AND DISCUSSION

Table 10 Results Of Final Product Tesing

SR.NO.	PARAMETERS		RESULTS		
	BATCH		GA-01	GA-02	GA-03
1	Average weight (gm)		0.3598	0.3597	0.3615
2	Uniformity if weight (gm)		0.3605	0.3605	0.3615
3	Hardness (N)		94	93	94
4	Thickness (mm)		4.2	4.3	4.2
5	Friability (% w/w)		0.44	0.65	0.53
6	Disintegration time (min: sec)		2.05	2.18	2.48
7	Assay of tablet (%)	RIFA	100.0	97.2	97.9
		INH	98.1	98.8	99.5
7	Dissolution (%)	RIFA	93	94	93
		INH	91	89	90

CONCLUSION

This study proves that Rifampicin is not only prone to hydrolysis and oxidation, but it can also react (indirectly though acid degradation or directly) with isoniazid to form a hydrazone. This interaction and degradation of Rifampicin can be reduced and the stability can be enhanced by two separate wet granulation processes, one for Rifampicin and the other for Isoniazid, the physical contact between these two drugs can be prevented. All results of evaluation parameters of tablets such as average weight, disintegration time, dissolution, friability, hardness, thickness was found satisfactory results and gives patient compliance.

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