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DESIGN AND *IN-VITRO* EVALUATION OF ORAL POROUS MATRIX TABLET FOR CONCOMITANT CONTROLLED RELEASE OF ANTI TUBERCULAR DRUGS

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ABSTRACT

Mycobacterium tuberculosis is a causative organism of tuberculosis, which is the most deadly disease after cancer in the current decade. The development of multidrug and broadly drug- resistant strains makes the tuberculosis problem more and more critical. The present study focused to develop an anti-tubercular (TB) fixed dose combination (FDC) tablet containing Rifampicin (RIF) and Isoniazid (INH) which would allow controlled delivery of RIF and INH. The preformulation studies were performed on RIF and INH, alone and in combination with excipients. The pharmacopoeia attributes of the FDC tablets were evaluated for Hardness, Friability, Weight variation and Thickness. The FDC matrix tablet was analyzed for the drug content and cumulative release of the drug. Fourier transform infrared, x-ray diffraction and differential scanning calorimetry results revealed that no relevant incompatibilities were identified in the kneaded system containing RIF, INH and Excipient. *In vitro* drug release from the FDC matrix tablet revealed that the polymer combinations rendered a cumulative dissolution of RIF and INH in acidic media with a controlled release pattern. The two polymer combinations used are found to be effective matrix for the release of both the drugs. This finding suggested that RIF and INH can be given by fixed dose combination by using two polymer combinations as matrix.

KEYWORDS: Fixed dose combination, Rifampicin, Isoniazid, Controlled release tablet, Tuberculosis.

INTRODUCTION

Tuberculosis (TB) is a transmittable disease caused by the infection with bacteria *Mycobacterium tuberculosis*. It is a major cause of mortality in recent years.[1] Although more than 20 anti-TB drugs and Bacille Calmette Guerin (BCG) vaccines are available for the treatment of tuberculosis, still tuberculosis is presenting a global challenge to human beings. *Mycobacterium tuberculosis* (*M. tuberculosis*) is the disease-causing agent of the disease tuberculosis.[2] It is one of the major killers of human beings in the current decade, according to World Health Organization it kills almost 2 million people every year with at least 9 million peoples are infected with TB.[3] *Mycobacterium tuberculosis (M. tuberculosis)* is mainly accountable for tuberculosis (TB), a deadly disease affecting one-third of the world population. *Human Immuno-deficiency Virus* (HIV) that develops in Acquired Immune Deficiency Syndrome (AIDS) has provoked the prevalence of TB, causing 50% of deaths among the HIV-infected patients due to co-infection with *M. tuberculosis*, thereby increasing the subside rate of the immune system.[4]

Anti-TB drugs can be administered as single-drug formulations or as fixed dose combination (FDC) formulations, combining two or more drugs in fixed proportions within the same formulation. Considering the severity and the spread of disease, World Health Organization (WHO) implemented the use of FDC as part of the control strategy to ensure that TB was adequately treated. This reduces the risk of drug resistance and also helps reduce the possibility of further TB transmission.[5-10]

Hydroxy propyl methylcellulose (HPMC) based monolithic hydrophilic matrix tablets that contain RIF and INH could provide sufficient initial release and extend release for up to 24 h for two of the drugs. It has been proposed that a tailored delivery system in which RIF is released in the stomach and INH is released in the intestine could be developed. Thereby, a matrix tablet which is produced with a reduced number of unit processes and using low-cost manufacturing process may provide a new approach for developing effective anti-tubercular FDC tablets.[11-13]

The goal of this study was to investigate the feasibility of formulating an anti-TB FDC tablet containing an immediate release layer (IRL) composed of RIF and a retarded release layer (RRL) composed solely of INH, which would allow the segregated delivery of RIF and INH.

MATERIALS AND METHOD

Selection of Granulation Method

By surveying the literature, wet granulation method was selected for formulation of matrix granules because of its key advantages and specifications.[20,21] In this method granules of Rifampicin and Isoniazid were prepared. Granules were prepared with different polymer concentrations by order. Micro-crystalline cellulose was used as the binding agent, Mg. Stearate and Lactose as gliding and lubricating agent in granules with its safety proven.

EXPERIMENTAL DESIGN

Central composite design

A three factor with three level central composite design was employed and the experimental runs were performed at all 14 possible combinations as suggested by Design Expert. The investigated independent variables were concentration of HPMC K4M (X_1), concentration of Carbopol 934 (X_2) and concentration of SB (X_3), while floating lag time (FLT) (Y_1), mucoadhesive time (Y_2) and Drug release at 10 h (Y_3) used as dependent variables.

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From the literature studies, the combination 6-14% of HPMC and Eudragit RS 100 shows good controlled release pattern. Higher and lower levels of HPMC: Eudragit RS100 was selected for central composite Design.

Statistical analysis

Statistical analysis of the central composite design batches was performed by multiple regression analysis using Microsoft Excel. To evaluate the contribution of each factor with different levels to the response, the two-way analysis of variance (ANOVA) was performed using the Design Expert 10 DOE demo version software.

Checkpoint analysis

A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken at 3 points, 1 from each contour plot, and the theoretical values of drug release were calculated by substituting the values in the polynomial equation. Matrix tablet was prepared experimentally at 2 checkpoints and evaluated for the responses.

Formulation development

Tablets of RIF and INH were prepared by using a Rotary Tablet press (MC-200; Rotary Tab, Ahmadabad) fitted with 10 mm round standard concave punches.

EVALUATION OF TABLET

Drug content

Five tablets were weighed individually and these tablets were crushed in a mortar. Drug equivalent to 10 mg of powder was taken, to this 10 ml of distilled water was added. The mixture was heated to melt (as per melting point of meltable binders) and allowed to cool to room temperature. The lipid was solidified and drug solution was filtered through Whatmann No.1 paper. The absorbance was measured at 224 nm after suitable dilution. The drug content was determined.[14]

***In Vitro* Drug Release Studies[15]**

In-vitro drug release study for the prepared matrix tablets was conducted for period of 12 hours using a fourteen-station USP XXVII type I (basket) apparatus at 37°C ± 0.5°C and 100 rpm speed. Also the *in-vitro* drug release study for the marketed tablets (R-cinex 300 mg) was conducted.

EXECUTION OF DISSOLUTION DATA

Model-independent methods to compare dissolution profiles

For the determination of dissolution data equivalence, FDA guidance documents recommend approaches such as the model-independent approach based on the calculation of difference (f1) and similarity (f2) factors, which is currently applied.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} [R_t - T_t]}{\sum_{t=1}^{n} R_t} \right\} \times 100$$

The dissolution profiles of products were compared using f2. The similarity factor is calculated by following formula.

$$f_2 = 50 \log \left\{ \left(1 \div \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\}$$

Dissolution profiles were compared using statistical evaluation of dissolution efficiency (DE). DE is defined as the area under the dissolution curve between two time points expressed as a percentage of the curve at maximum dissolution, 100%, over the same time period.

$$DE = \int y \frac{dt}{100t}$$

DE was calculated from the area under the dissolution curve at 240 min and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. Each formulation was compared with the same formulation prior to keep for stability study at time zero, after 1 (1M) and 3 (3M) months, using similarity factor f2. Furthermore, DE values were determined to evaluate the effect of aging conditions on the dissolution stability within each formulation. The results were mentioned in table 2.

RESULT AND DISCUSSION

Central composite experimental design

In this design 2 factors will be evaluated, each at 3 levels as shown in table, and experimental trials will be performed at all 13 possible combinations. The percentage of HPMC: Eudragit RS 100 was selected as factors. Statistical analysis of the central composite design batches was performed by multiple regression analysis using Design Expert.

Table 1: Polymer levels.

Level	Polymer quantity(mg)
High	80
Intermediate	60
Low	40

Data analysis

A Central composite statistical design with 2 factors, 3 levels and 13 runs was selected to study the effects on dependant variables. All the batches of prepared tablet within the experimental design yielded tablet and these were evaluated for drug release media.

Probability plots

Probability explain the whether the residuals follow a normal distribution, in which case the points will follow a straight line. The results are shown in Figure 1 and 2.

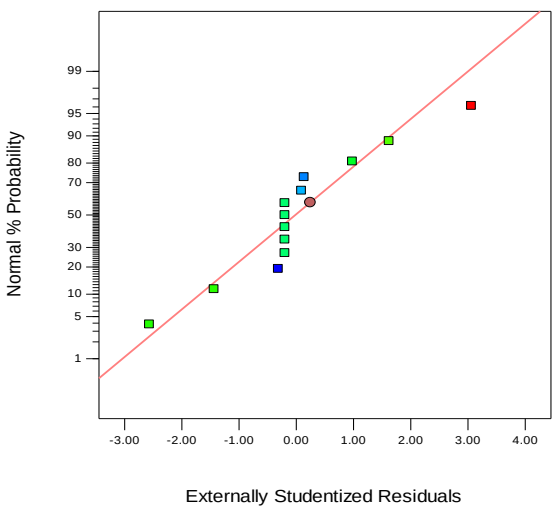

Fig. 1: Normal plot of residuals of % cumulative drug release RIF.

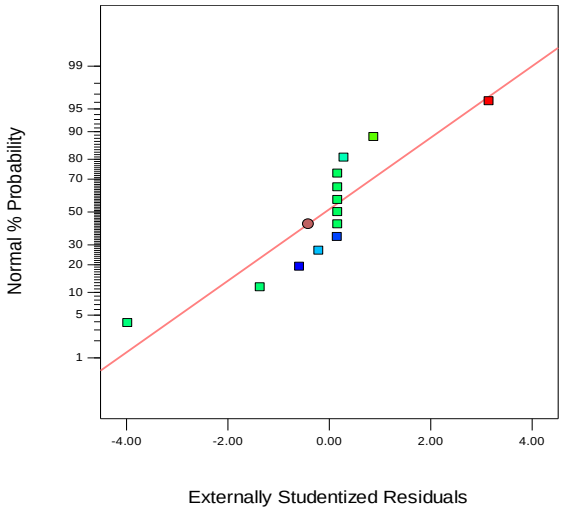

Fig. 2: Normal plot of residuals of % cumulative drug release of INH

EVALUATION OF TABLET

Physiochemical parameter

The comparison of physical properties of the matrix tablets is shown in Table 2 the percentage of drug content was more than 91 %. The results also showed acceptable and homogenous distribution of drug in tablets.

Table 2: Evaluation parameters of the tablet.

Batch Code	Avg. wt (mg)	Hardness Kg/cm^2	Thickness (mm)	Friability %	Drug content %	
					RIF	INH
B1	600.00±1	9.87±0.12	4.10±0.10	0.39±0.19	93.54±0.011	93.44±0.006
B2	600.33±2.08	10.13±0.21	4.13±0.21	0.89±0.53	91.57±0.07	94.22±0.008
B3	601.00±2.65	10.10±0.50	4.17±0.12	0.39±0.10	95.06±0.018	97.61±0.008
B4	597.33±2.08	9.97±0.46	4.20±0.10	0.33±0.29	93.02±0.025	92.46±0.006
B5	601.67±2.08	10.20±0.40	4.27±0.06	0.44±.10	91.59±0.030	91.64±0.006
B6	602.33±0.58	10.20±0.30	4.07±0.12	0.66±0.60	91.75±0.013	96.32±0.012
B7	599.67±5.51	9.97±0.21	4.13±0.06	0.33±0.16	91.87±0.003	94.07±0.006
B8	603.00±1	10.30±0.20	4.10±0.10	0.39±0.10	93.57±0.012	91.75±0.008
B9	599.00±1.73	9.87±0.12	4.13±0.15	0.33±0.29	92.35±0.027	94.81±0.012

In vitro Dissolution studies

According to the literature, the amount of drug dissolved from modified release tablets must exceed 90% in 3-4 hr therefore; the resulted dissolution profile met the above mentioned requirement. Fig. 3 and 4 indicates *in vitro* dissolution of RIF and INH respectively.

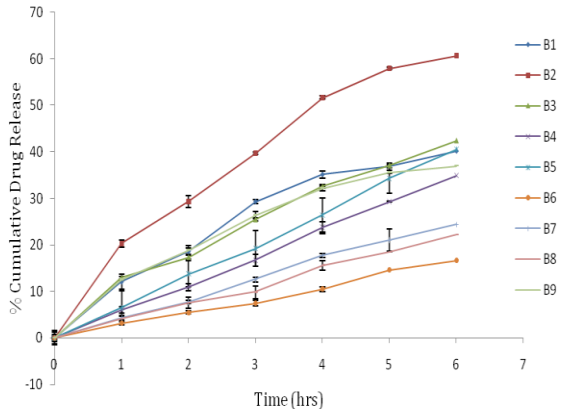

Fig.3: Comparison of in vitro release profile of RIF

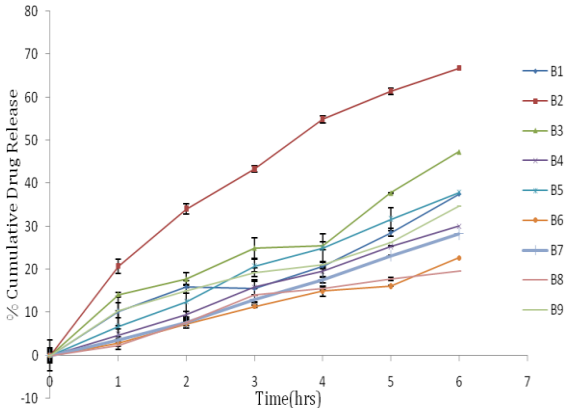

Fig.4: Comparison of in vitro release profile of INH

Comparison with marketed formulation

From release profile f1 and f2 factors calculated. The values of f1 and f2 factors for RIF and INH are within limits. Therefore, formulated formulation was found to be bioequivalent with marketed formulation.

Table 3: Dissolution comparison Profiles throughout the accelerated* Aging Study.

Storage Time	Parameter	Formulation Code	
		B 3	
		RIF	INH
0 M	$t_{\%}$ release	43.96	47.33
	Assay	95.06	97.61
	f_1	2.57	7.55

	f_2	55.94	32.75
	Dissolution Profile	Similar	Not Similar
3 M	$t_{\%}$ release	45.11	47.00
	Assay	95.20	96.11
	f_1	1.16	4.22
	f_2	72.47	45.31
	Dissolution Profile	Similar	Not Similar
6 M	$t_{\%}$ release	45.11	47.00
	Assay	34.21	97.20
	f_1	0.57	3.08
	f_2	85.53	52.09
	Dissolution Profile	Similar	Similar
*Accelerated- 40°C/75% RH			

CONCLUSION

The control release matrix tablet can be used as an alternative to conventional dosage forms for the FDC of drugs RIF and INH. From the present experimental result it can be concluded that release of RIF and INH from the matrix tablet is in controlled manner. The formulation prepared with the combination of HPMC and Eudragit RS100 showed better *in vitro* drug release pattern, drug content, hardness. Optimized formulation was found to be stable for a period of 6 months.

From the above experimental data it can be concluded that a successful controlled release matrix tablet having FDC of RIF and INH have been developed by using combination of HPMC and Eudragit RS100 for the treatment of TB.

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