International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

A novel drug delivery system designed for modulating the release kinetics of anti-tubercular drugs

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ABSTRACT

The major clinical issue with TB therapy is the poor oral bioavailability of rifampicin in the presence of isoniazid in acidic medium. The present work was undertaken to develop a novel solid dosage form (tablet and capsule in capsule) comprising a immediate release rifampicin tablet, effervescent gastro retentive rifampicin tablet and an enteric coated isoniazid capsule that can differentiately release rifampicin in a controlled manner in the stomach and isoniazid in the intestine. Rifampicin GRDDS was formulated using different concentrations of HPMCK4M and HPMCK100M as matrixing agent. Enteric coated isoniazid capsule was formulated using eudragit L100-55. Drug release and drug degradation of the novel dosage form was compared with R-Cinex. About 42% of rifampicin was degraded to 3FRSV from R-Cinex at the end of 60 mins whereas only 10% of rifampicin degraded in case of novel dosage form. Hence, the minimization of contact between rifampicin and isoniazid by sustaining the release of rifampicin can alleviate its degradation to a certain extent.

Keywords: Bioavailability, Controlled release, Isoniazid, Rifampicin, Tuberculosis.

INTRODUCTION

Rifampicin and isoniazid are the mainstays of the tuberculosis therapy during the last forty years. Rifampicin is the single drug that has the major capability to kill dormant tubercular bacilli. Over the years, FDCs have emerged with two serious problems that include: the poor and impaired bioavailability of rifampicin in combination with isoniazid from FDC formulations and the poor stability of rifampicin containing FDC's is the second major problem [1]. Drug resistant TB and treatment failure are because of the use of these substandard FDC [2]. It has now been justified that rifampicin interacts with isoniazid in the acidic medium of the stomach to form inactive isonicotinyl hydrazone. Shishoo *et al*, have shown that the extent of interaction of rifampicin with isoniazid in the acidic environment of the stomach leading to about 8.5 to 50% of rifampicin degradation [3]. This results in the poor bioavailability of rifampicin from the FDCs. Hence, there is a critical need to redesign the currently available anti- TB FDCs. In order to avoid interaction between rifampicin and isoniazid, both in formulation as well as *in vivo*, a novel anti-TB FDC formulation is proposed, wherein, rifampicin and isoniazid will be released in different regions of the GIT. The total dose of rifampicin was subdivided into two components. One is immediate release tablet of rifampicin containing the loading dose of rifampicin and the second one is gastro retentive floating tablet of rifampicin containing the maintenance dose of rifampicin. A novel solid dosage form was formulated by placing an immediate release rifampicin tablet, gastric floating rifampicin tablet and an enteric coated isoniazid capsule of size '4' capsule together were put into a hard gelatin capsule of size "00". The prepared novel solid dosage form was evaluated for *in vitro* drug release studies.

Floating hydrophilic matrix tablets of rifampicin were prepared by direct compression technique using different concentrations of HPMCK4M and HPMCK100M as matrixing agent and sodium

bicarbonate was used as the gas generating agent. All the ingredients were blended in glass mortar pestle uniformly excluding magnesium stearate. After ensuring the uniform mixing of drug as well as other excipients, magnesium stearate was added finally and allowed for further mixing of 2-3 mins before punching. The floating hydrophilic matrix tablets of rifampicin were analyzed to determine their hardness, friability, weight variation, % composition, floating property study (FLT and TFT) and *in vitro* drug release studies. Immediate release tablets of rifampicin are prepared by direct compression method. All the ingredients were blended in glass mortar pestle uniformly excluding magnesium stearate. After ensuring the uniform mixing of drug as well as other excipients, magnesium stearate was added finally and allowed for further mixing of 2-3 mins before punching. The immediate release tablets of rifampicin were analyzed to determine their hardness, friability, weight variation, % composition, disintegration time and *in vitro* drug release studies. Enteric coated hard gelatin capsules (size 4) containing a compacted mass of isoniazid (100 mg) and dicalcium phosphate dihydrate (50 mg) were prepared by coating with eudragit L-100 using the dip coating technique.

Both the drug release and degradation of the prepared novel solid dosage form was compared with marketed formulation (R-Cinex). It was observed that about 42% of degradation to 3FRSV occurs from R-Cinex at the end of 60min whereas only 10% of degradation of rifampicin occurs in the case of novel solid dosage form. Thus, rifampicin release kinetics had been modulated in this novel design so as to target it to the stomach *via*, gastro retention approach, and floating drug delivery systems. A part of rifampicin dose was formulated as a loading dose in the form of immediate release tablet. Loading dose of rifampicin will be released immediately in stomach followed by its sustained release maintained through the maintenance dose as gastro retentive floating formulation. Sustaining the release of rifampicin in stomach will help to maintain the concentration of rifampicin within therapeutic window, at its absorption maxima site for a prolonged period of time. The sustained release delivery systems hold a promising approach in the management of tuberculosis by reducing the dosing frequency and improving patient compliance.

EXPERMENTAL

Materials*:* Rifampicin and isoniazid was a gift sample provide by Lupin Pharmaceuticals Ltd., Ahmedabad, Hydroxypropylmethylcellulose (HPMC) was purchased from Dow chemical, USA, sodium bicarbonate was obtained from Hercules, USA and eudragit L1100-55 was provided by Aizant Pharmaceuticals, Hyderabad. Microcrystalline cellulose PH101 (MCC) was obtained from Hetero Pharmaceuticals, Hyderabad. Di calcium phosphate dihydrate, sodium starch glycolate, mannitol, castor oil, titanium dioxide and Magnesium stearate were of analytical reagent grade. Size ‘4’ and size ‘00’ capsules were obtained from Finoso Pharmaceuticals Pvt. Ltd., Hyderabad.

Preparation of novel drug delivery system

Formulation development of rifampicin: Formulation development of rifampicin is subdivided in two parts, wherein,

Part A: Formulation development of immediate release tablet of rifampicin (*loading dose).*
Immediate release tablets of rifampicin are prepared by direct compression method. All the ingredients except magnesium stearate were blended in glass mortar pestle uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate was added and further mixed for additional 2-3 mins. The tablets were compressed using 6mm concave punch on a single stroke punching machine. The composition of the formulation is given in Table 1.

Part B: Formulation development of gastro retentive floating tablet of rifampicin (*maintenance dose*).
Floating hydrophilic matrix tablets were prepared by direct compression technique using different concentrations of HPMCK4M and HPMCK100M as matrixing agent, sodium bicarbonate as gas generating agent. All the ingredients except magnesium stearate were blended in glass mortar pestle uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate was added and further mixed for additional 2-3 mins. The tablets were compressed using 6mm concave punch on a single stroke punching machine. The composition of the formulation is given in Table 2.

Formulation of enteric coated isoniazid capsule: Hard gelatin capsules (size 4) containing a compacted mass of 100 mg of isoniazid and 50 mg of dicalcium phosphate dihydrate were coated using the dip coating technique. The coating solution was prepared by dissolving 2 g of eudragit L100-55 in 100 mL of isopropyl alcohol. Castor oil (10% wt/wt of eudragit L100-55) and titanium dioxide (20% wt/wt of eudragit L100-55) were mixed with the solution under stirring at 100 rpm. The volume of coating dispersion was adjusted to 100 mL using isopropyl

alcohol. The weight gain of the capsule was attributed to the amount of eudragit L100-55, titanium dioxide, and castor oil in the film.

Preparation of novel drug delivery system: Novel dosage form was formulated by placing an immediate release rifampicin tablet, gastric floating rifampicin tablet and an enteric coated isoniazid capsule of size '4' capsule together were put into a "00" size hard gelatin capsule.

Analysis of formulation

Evaluation of rifampicin: Evaluation of rifampicin is subdivided in two parts, wherein,

Part A: Evaluation of immediate release tablet of rifampicin (*loading dose).*

The hardness, disintegration time and friability of the tablets were measured in a hardness tester (Pfizer, Mumbai), disintegration testing apparatus (Electrolab, Mumbai) and friabilator (Electrolab, Mumbai) respectively. The uniformity of drug content of all batches (10 units tablets) was analyzed in a spectrophotometer (model UVPC 1601, Shimadzu, Japan), in a 1 cm quartz cell, at 475 nm.

Rifampicin release from immediate release tablets prepared was studied using USP type II (paddle) 8 station dissolution testing apparatus (Lab India, Disso) at 100 rpm, 37±0.5°C and 0.1N HC was used as dissolution medium. A sample (10ml) of solution was withdrawn from the dissolution apparatus at regular intervals and the same volume was replaced with fresh dissolution medium to maintain sink conditions. Rifampicin and 3FRSV (degradation product of rifampicin) were determined by the dual wavelength spectrophotometric method in the chloroform layer [4].

Part B: Evaluation of gastro retentive floating tablet of rifampicin (*maintenance dose*).

The weight variation and friability of the tablets were measured in an electronic balance (Shimadzu, Mumbai) and friabilator (Electrolab, Mumbai) respectively. The uniformity of drug content of all batches (10 units tablets) was analyzed in a spectrophotometer (model UVPC 1601, Shimadzu, Japan), in a 1 cm quartz cell, at 475 nm. The floating lag time and Total floating time of each batch was done in triplicate using USP type II dissolution apparatus (Electrolab, Mumbai) containing 900ml of 0.1N HCl using paddle at a rotational speed of 100 rpm. The temperature of the medium was maintained at 37 ± 2°C.

An *in vitro* release study was carried out to evaluate their performance as rate-controlling agents. Rifampicin release from floating matrix tablets prepared was studied using USP type II (paddle) 8 station dissolution rate testing apparatus (Lab India, Disso) at 100 rpm and at a temperature of 37±0.5°C. The dissolution medium used was 0.1N HCl and pH 7.4 phosphate buffer was used as dissolution medium. A sample (10ml) of solution was withdrawn from the dissolution apparatus at regular intervals and the same volume was replaced with fresh dissolution medium to maintain sink conditions. Rifampicin and 3FRSV (degradation product of rifampicin) were determined by the dual wavelength spectrophotometric method in the chloroform layer.

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration [5]. The first order Eq. (2) describes the release from system where release rate is concentration dependent [6]. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3) [7]. The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets [8].

$$C = k_o t \quad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - kt / 2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$Q = Kt^{1/2} \quad (3)$$

Where, K is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t \quad (4)$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made: *cumulative % drug release vs. time* (zero order kinetic model); *log cumulative of % drug remaining vs. time* (first order kinetic model); cumulative *% drug release vs. square root of time* (higuchi model) *log cumulative % drug release vs. log time* (koresmayer model) and *cube root of drug % remaining in matrix vs. time* (hixson-crowell cube root law).

Koresmayer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5) [9]. To find out the

mechanism of drug release, first 60% drug release data was fitted in Koresmayer–Peppas model:

$$M_t / M_\infty = Kt^n \quad (5)$$

Where M_t / M_∞ is the fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanism, where for cylinder value of n is 0.43 indicate fickian diffusion, between 0.43 and 0.85 indicate anomalous transport and > 0.85 indicate case II transport.

Evaluation of novel drug delivery system: The novel dosage form was evaluated for *in-vitro* drug release studies. The dissolution test was carried out using USP apparatus II (Labindia, Mumbai) up to 12 h. The temperature was maintained at 37 ± 0.5°C and the rotation speed was 50 rpm. The dissolution medium used was 350 ml simulated gastric fluid, 0.1N HCl (pH 1.2) for initial 2 h of the study, and then the total media was replaced with 900ml, pH 7.4 phosphate buffer up to12 h. At suitable intervals, 10 ml samples were withdrawn, filtered, diluted appropriately with the medium. The volume withdrawn at each time interval was replaced with fresh quantity of the dissolution medium. Rifampicin and 3FRSV (degradation product of rifampicin) were determined by the dual wavelength spectrophotometric method in the chloroform layer [4]. Isoniazid was measured by the spectrophotometric method at λ_{max} 263 nm respectively [10]. The mean cumulative percent of drug release of six tablets from three different batches was calculated, and was used in the data analysis. Drug release and drug degradation of the novel dosage form was compared with R-Cinex.

RESULTS AND DISCUSSION

Evaluation of rifampicin tablets: Evaluation of rifampicin is subdivided in two parts, wherein,

Evaluation of immediate release tablet of rifampicin: The physic-chemical properties of rifampicin immediate release tablets are tabulated in Table 3.
The % cumulative drug release was calculated (in triplicate) and plotted over time, which is depicted below in Fig-1.

Evaluation of gastro retentive floating tablet of rifampicin: Hardness of the tablets was in the range of 4-6kg/sq.cm. Weight loss in the friability test was less than 0.48% in all the cases. All the matrix tablets prepared contained 98±2.5% of the labeled claim. All the tablets were found to be non-disintegrating in acidic pH 1.2. As such, the prepared tablets were of good quality with regard to drug content, hardness and friability (Table 4). As the tablets formulated were non-disintegrating in acidic and alkaline fluids, they are considered suitable for gastro retentive drug delivery system.

Rifampicin release from matrix tablets prepared was studied in simulated gastric fluid for 12 h. Drug release profiles of rifampicin matrix tablets are shown in Fig-2. Rifampicin release was relatively rapid in case of matrix tablets prepared employing 10%HPMCK4M. The floating lag time of 60 sec and a total floating time of 5 h for 100.30% were observed for these tablets. When 15% of HPMCK4M was used in the formula, the release at the end of 8th hour is 101.34%. The matrix tablets containing 20%HPMCK4M released 99.73% at the end of 10^{th} h while the matrix tablets containing 5%HPMCK100M released 100.56% at the end of 8^{th} h. The matrix tablets containing 10%HPMCK100M showed 99.78% drug release at 10^{th} h. When 15%HPMCK100M was used in the formula the drug release at the end of 12^{th} h was found to be 99.71% while those containing 20%HPMCK100M in the formula released a minimum amount of 91.95% at the end of 12^{th} h. The floating of the tablet was attributed to the presence of hydroxypropyl methylcellulose K100M and to gas formation resulting from the chemical reaction between sodium bicarbonate and hydrochloric acid. The gelling property of hydroxypropyl methylcellulose K100 M is responsible for sustaining drug release from the matrix tablet [11]. The drug release from swellable and erodible hydrophilic matrices can be attributed to polymer dissolution, drug diffusion through the gel layer, or a combination of both [12]. Rifampicin release from the prepared matrix tablets was fast in high polymer concentrations and release decreased with increase in polymer concentrations up to certain period. So, the formulation F6 was considered optimum for floating controlled release following zero order kinetics and diffusion release.

The drug release data were analyzed as per zero order, first order, higuchi and peppas equation models. Analysis of release data as per zero order and first order kinetic models indicated that the rifampicin release from the matrix tablets followed zero order kinetics. The correlation coefficient (r) values were higher in the zero order models than the first order models. The drug release pattern is found to be following higuchi and koresmayer peppas model kinetics (r = 0.951 and r = 0.992 respectively). Hence the drug release from the formulation F6 is showing that the release pattern of the drug is diffusion controlled.

Evaluation of novel drug delivery system: The molecular weights of rifampicin and 3FRSV are 823 and 726, respectively. The molecular weights are dissimilar so the method reported by Lukulay and Hokanson can be used for back-calculating the amount of rifampicin that underwent degradation to 3FRSV.

The following formula was used:
Percentage Rifampicin Degraded = Percentage of 3 FRSV Formed*(823/726)

One of the objectives of the present study was to gradually release the rifampicin in acidic medium to minimize the concentration-dependent degradation of rifampicin. Rifampicin is soluble in acidic medium, and it is also absorbed throughout the gastrointestinal tract. Therefore, a higher percentage of rifampicin bioavailability may be expected if it is assumed that the process of rifampicin absorption is faster than the process of its dissolution. Results show that 42% of rifampicin was degraded to 3FRSV from the R-Cinex capsule containing rifampicin and isoniazid at 60 mins. On the other hand, only 10% of rifampicin was degraded from the novel dosage form containing the enteric-coated isoniazid capsule and the floating tablet of rifampicin at 60 mins. The higher percentage of degradation R-Cinex capsule may be attributed to the triggering action of isoniazid. The results of the present study underline the fact that minimization of contact between rifampicin and isoniazid results in less degradation of rifampicin. Enteric coating of isoniazid, therefore, is justified. Isoniazid is poorly soluble in chloroform (0.1 g/100 mL). Hence, it was analyzed in aqueous medium and in chloroform layer for the first 2 h. As expected, isoniazid was not released in acidic medium from the enteric-coated isoniazid capsule. Castor oil, a hydrophobic plasticizer, prevents dissolution of the enteric coat in acidic medium. More than 90% of isoniazid was released in alkaline medium in 30 mins. It is worthwhile to note that isoniazid is well absorbed from the GIT. The isoniazid capsule was taken out of the dissolution vessel after 2 h for further dissolution study in phosphate buffer (pH 7.4). Rifampicin and 3FRSV (degradation product of rifampicin) were determined by the spectrophotometric method in the chloroform layer. Isoniazid was measured by the spectrophotometric method at λ_{max} 263nm.

CONCLUSION

Gastro retentive rifampicin tablets can be formulated to increase the gastric residence time and thereby increase the oral bioavailability. Formulation F6 gave better controlled release and floating properties in comparison to the other formulations. Rifampicin floating tablets followed zero order release with diffusion controlled release mechanism. Rifampicin immediate release tablets were formulated as the loading dose of rifampicin to maintain sufficient drug plasma concentrations. Formulated tablets showed satisfactory results for their evaluations like hardness, weight variation and *in-vitro* drug release. Enteric coated isoniazid size '4' capsule was formulated using eudragit L100-55 as enteric coating polymer. Novel dosage form was formulated by placing an immediate release rifampicin tablet, gastric floating rifampicin tablet and an enteric coated isoniazid capsule in a size '4' capsule. Drug release and drug degradation of the novel dosage form was compared with R-Cinex. It was found that 42% of Rifampicin was degraded to 3FRSV from R-Cinex at the end of 60mins whereas only 10% of Rifampicin degraded in the case of novel dosage form. Hence, the minimization of contact between rifampicin and isoniazid and sustained release of rifampicin can alleviate the degradation of rifampicin to a certain extent from the novel dosage form. This novel dosage form will be the preferred formulation owing to less degradation of rifampicin.

ACKNOWLEDGEMENTS

The authors are grateful to the University Grants Commission, New Delhi, India for granting junior research fellowship in engineering and technology, to carry out this work. The authors would like to express their gratitude to M/s Lupin Pharma Pvt. Ltd. for supplying the gift sample of rifampicin and isoniazid.

Table 1. Composition of immediate release tablets of rifampicin

Ingredients	Quantity(mg)
Rifampicin	100
Sodium starch glycolate	8
MCC	10
Mannitol	27
Magnesium stearate	5

Table 2. Composition of floating tablets of rifampicin

Batch	Drug (mg)	HPMC K4m (mg)	HPMC K100m (mg)	NaHCO3 (mg)	Magnesium Stearate (mg)	Avicel (mg)	Total (mg)
F1	100	15	-	15	2	20	152
F2	100	22.5	-	15	2	10.5	152
F3	100	20	-	15	2	13	152
F4	100	-	7.5	15	2	25.5	152
F5	100	-	15	15	2	18	152
F6	100	-	22.5	15	2	10.5	152
F7	100	-	30	15	2	3	152

Table 3. Physico-chemical evaluation of immediate release tablets of rifampicin

Description	Red, oval shaped
Hardness(Kg/cm2)	4±0.65
Average Weight(mg)	150±0.84
Assay values (%)	96.86±0.57
Disintegration time(sec)	2.12±0.034

Table 4. Physical evaluation of rifampicin floating tablets

Batch	Average weight(mg)	Friability (%)	Assay (%)	Floating lag time (sec)	Total floating time (hrs)
F1	150±0.83	0.54±0.03	96.14±0.45	60	5
F2	150±1.23	0.59±0.09	96.89±0.57	58	8
F3	150±0.50	0.48±0.08	98.58±0.42	70	10
F4	150±0.99	0.67±0.12	99.02±0.63	75	8
F5	150±1.68	0.53±0.06	98.06±0.54	62	10
F6	150±0.78	0.49±0.08	99.23±0.55	60	12
F7	150±0.89	0.46±0.04	96.95±0.68	78	>12

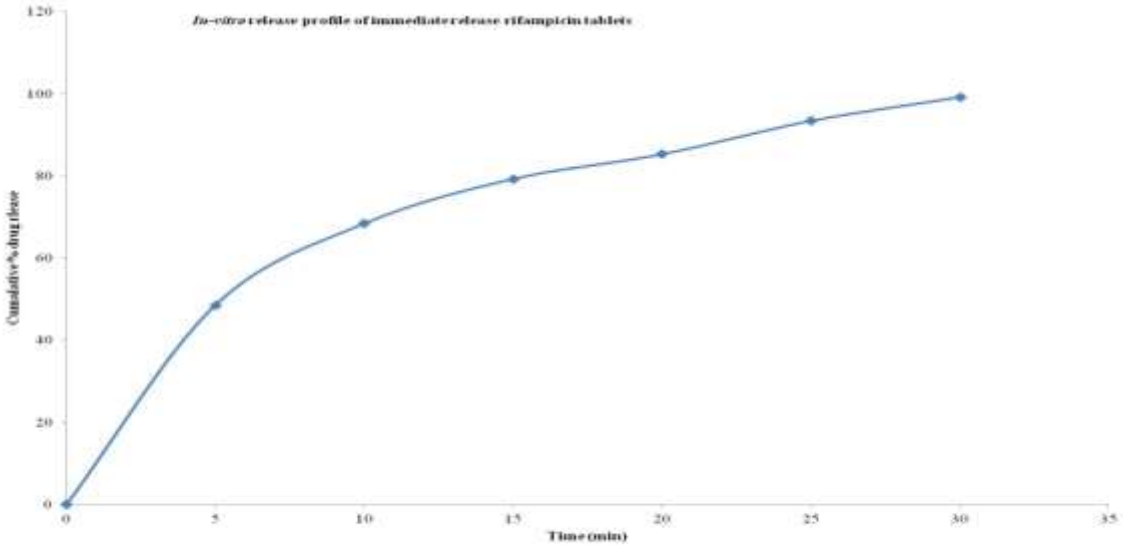

Fig. 1: *In-vitro* release profile of rifampicin from immediate release tablets
(Each point represents mean± SE, n=3)

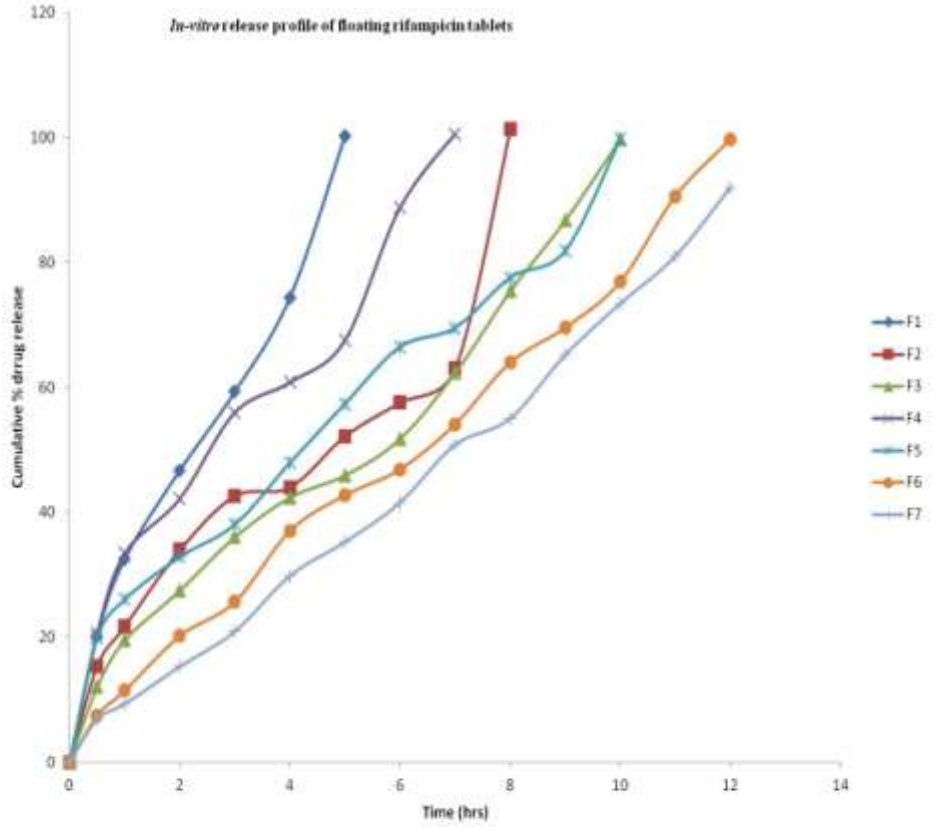

Fig. 2: *In-vitro* release profile of rifampicin from floating matrix tablets
(Each point represents mean± SE, n=3)

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