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Development of extended release matrices of rifampicin using hot melt extrusion technique

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ABSTRACT

Tuberculosis has metamorphosized over the decades from drug resistant to multidrug resistant to the lethal extensively drug resistant forms lately. With scarce newer anti-TB drugs emerging, there is a pressing need to ameliorate the current treatment therapy by modulating the formulation approaches towards the first line treatment drugs. In the present study an attempt has been made to formulate Rifampicin (RIF), the first line treatment drug for TB as an extended release oral formulation using melt extrusion technique. The total dose of RIF was divided into two components- Immediate release (IR) pellets of RIF as the loading dose (300mg) and extended release tablet as the maintenance dose (150mg). Extrusion trials were conducted using various class of extrudable polymers (cellulose, polyvinyl acetate, polyethylene oxide, poly(meth)acrylates). Based on the preliminary findings, IR pellets were formulated using Eudragit EPO whereas hydroxylpropyl cellulose (HPC) was further explored as the matrix former. The release rate was modified using addition of hydrophilic pH independent release modifier. The formulation was characterized with respect to *in vitro* dissolution behavior, thermal and chemical stability, miscibility, drug-polymer interactions and surface morphology followed by stability studies. The loading dose could adequately release RIF initially whereas a combination of hydrophilic pH independent polymer of varying viscosity could successfully control RIF release over 24 hours following zero order release mechanism. The developed formulation exhibited content uniformity, physical and chemical stability over a period of six months. The application of melt extrusion for developing extended release matrices for anti-TB drugs like RIF was sought. Melt extrusion being a continuous manufacturing process could be scaled up commercially thus enhancing the feasibility of the designed formulation.

INTRODUCTION

Tuberculosis (TB) continues to pose as a global menace despite of a myriad of attempts worldwide. Moreover, the emergence of multiple/extensive/total drug resistant cases of TB and HIV co infection are major threats to the control of the disease. Keeping in view that TB is a global emergency, the formulation research strategies should focus on overcoming the aforementioned challenges by adopting newer delivery approaches for anti TB drugs.

Rifampicin (RIF), the semi synthetic hydrazine derivative of rifampicin B remains one of the classical first line drug for TB. In addition to a significant early bactericidal effect on metabolically active *M. tuberculosis*, RIF also exhibits excellent late sterilizing action on semidormant organisms undergoing short bursts of metabolic activity (Somoskovi et al., 2001).

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However, some of the challenges that the potent chemotherapeutic faces include relatively short biological half-life of 2-5 hours, increased hepatic metabolism, induction of a prehepatic first-pass effect, drug resistance and adverse effects due to multiple doses and above all patient noncompliance due to prolonged conventional treatment. Bioavailability of orally administered RIF decreased from 93% after the first single oral dose to 68% after 3 weeks of oral & iv RIF therapy which is attributed to both, an increased hepatic metabolism & induction of hepatic endoplasmic reticular enzymes (cytochrome P450s, mainly 3A4 isozyme) resulting from multiple RIF doses (Loos et al., 1985). Moreover for actives like RIF, formulations with relative lower rate of dissolution ought to show less decomposition and hence a better bioavailability (Singh et al., 2001). These pharmacokinetic considerations warrant the development of an extended release system which could release RIF in a controlled manner thereby overcoming the aforesaid obstacles.

For chronic diseases like TB, controlled drug delivery systems have potential advantages over conventional multiple dose systems. Attempts have been made previously to deliver RIF in an extended release manner using various approaches. RIF-loaded

PLGA nanoparticles having improved antibacterial efficacy were fabricated by an emulsification/solvent diffusion method (Esmaeili et al., 2007). An oral C.R. formulation has been developed based on poly (dllactide- co-glycolide) microparticles for the delivery of isoniazid, rifampicin, and pyrazinamide either individually or in combination (Ain et al., 2002). Alginate hydrogel microparticles were developed for oral controlled delivery of anti-tubercular drugs isoniazid, rifampicin and pyrazinamide alone and in combination (Ain et al., 2003). A colloidal dosage form for the oral delivery of rifampicin and isoniazid in combination was developed with the aid of artificial neural network (ANN) data modeling (Kustrin et al., 2003). Sustained release capsular systems for simultaneous delivery of rifampicin and isoniazid (an osmotically regulated multi-drug oral delivery system) comprising asymmetric membrane coating and dense semipermeable membrane coating was attempted to reduce the potential side effects and enhance patient compliance (Prabhakaran et al., 2004). Ethylcellulose coated nonpareil beads of RIF using propylene glycol and castor oil as plasticizers is also reported (Rao and Ramana, 2002). S.K. Mehta *et al.* investigated the potential of microemulsion composed of oleic acid, phosphate buffer, Tween 80 and ethanol as a controlled delivery system for RIF (Mehta et al., 2007). Liposomes and PLG microparticles were also evaluated as sustained release carriers for RIF and isoniazid (Dutt and Khuller, 2001). A thorough review of the literature reveals that an industrially feasible technique like melt extrusion has not been explored so far for developing extended release matrices of anti-TB drugs.

Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms due to their flexibility to provide a desirable drug release profile, nontoxicity, cost effectiveness, broad regulatory acceptance, ease of handling, ease of compression, ability to accommodate higher amount of drug, minimum influence of the processing variables on drug release rates and relatively simple tablet manufacturing technology making them excellent carriers for oral matrix tablets (Alderman, 1984; Lee et al., 1999).

Hot melt extrusion, a new wave stirring the pharmaceutical technology is known to possess significant potential as a continuous pharmaceutical manufacturing process. It has been proved to be an efficient technology for producing controlled release matrix/multiparticulate systems with considerable advantages over the conventional solid dosage form manufacturing processes. Some of the advantages include continuous process, reduced number of processing steps, suitability for drugs with low compressibility, solvent free/green technology, closed process unit etc. Moreover, it is capable of achieving less porous matrices thus reducing burst release in early hours. During the extrusion process, polymeric particles are softened and distorted by the rotating screw due to application of heat. On cooling, extensive solid bridges are formed between the particles resulting in a smaller pore radius and a more tortuous network thereby facilitating densification of the molten mass to a higher extent than compaction of the powder during compression (Crowley et al., 2004). Interestingly, these attributes have never been utilised to tackle challenges of current TB therapy.

The objective of the present work was to develop extended release formulation of RIF by hot melt extrusion technique. The research work undertook the following major formulation challenges: addressing pH dependent solubility of RIF, enhancing its stability and developing a melt extruded formulation with maximum drug loading.

MATERIAL AND METHODS

Materials

Rifampicin USP was received as gift sample from Lupin Laboratories Ltd (Pune, India), Kollidon®VA64 was generously gifted by BASF (Mumbai, India), Hydroxypropyl cellulose (Klucel® MF and LF Pharm grades) were kindly gifted by Ashland (Mumbai, India) and Eudragit® EPO was supplied as gift sample from Evonik Industries (Mumbai, India). Polyethylene glycol (PEG 400) was purchased from S.D fine chemicals. Other chemicals and solvents used were of analytical grade.

Design of the formulation

To comply with the biopharmaceutical requirement of achieving minimum effective concentration and to elicit the required therapeutic effect in the body, the total dose of formulation (450mg) was divided into two doses: loading dose of 300mg as melt extruded RIF immediate release (IR) pellets and maintenance dose of 150mg as melt extruded tablet. The selection of polymeric carriers and plasticizers was based on the preformulation studies and calculation of Hansen solubility parameters (data not shown).

Formulation of immediate release (IR) pellets

A powder blend containing 50%, w/w RIF and Eudragit EPO (pre plasticized with triethyl citrate-5%) was blended and processed by a single screw hot melt extruder (Lab Model, S.B Panchal & Co.) equipped with a 100 mm long and 20 mm diameter screw using the following parameters: extrusion temperature: 110°C, screw speed: 40 rpm, die diameter: 1mm and feed rate: 1g/min. The extrudates thus obtained were cooled to ambient temperature, cut into cylindrical pellets of 1 mm each and stored in HDPE containers until analysis.

Formulation of extended release (ER) tablet

Extrusion trials were taken using three viscosity grades of hydroxyl propyl cellulose (avg. molecular weight of MF: 850,000 and LF: 95,000) as the matrix former. RIF (50%, w/w) was melt extruded with various grades of Klucel® pre plasticized with propylene glycol (5%) using the following parameters:- extrusion temperature: 85°C, screw speed:40 rpm, die diameter: 5mm and feed rate: 1g/min. The residence time of the materials within the extruder was about 2 to 3 minutes. The extrudates thus obtained were cooled to ambient temperature, cut into tablets having weight equivalent to 150mg RIF and stored in HDPE

containers until analysis. The pellets equivalent to 300mg RIF and 150mg equivalent tablet were filled into size 00 gelatin capsules and subjected to further investigation

In vitro dissolution studies

The formulation was subjected to *in vitro* dissolution studies using the following protocol: dissolution apparatus: USP Type II (Electrolab), dissolution medium: simulated gastric fluid (SGF pH 1.2, 0.1N HCl) for initial 2 hours followed by pH 6.8 simulated intestinal fluid (SIFsp) containing 0.02% ascorbic acid at 37 ± 0.5°C till the end of 24 hours and stirring speed: 50 rpm. 5 ml of aliquots were withdrawn at predetermined intervals and replenished with dissolution medium. They were suitable diluted and analyzed using UV-spectrophotometer UV-1088 (Shimadzu, Japan) at 475nm.

Drug release kinetics

The dissolution data was fitted into various kinetic mathematical models: zero order, first order, korsmeyer-peppas and Higuchi equation and the best fit was decided on the basis of regression values.

Characterization of the developed formulation

The formulation was powdered and characterized with respect to thermal and chemical stability, miscibility, drug–polymer interaction and surface morphology as follows:

Thermogravimetric analysis

A TGA (TA Instruments, SDT Q600 V8.2 Build 100) was employed to investigate the thermal stability of the drug, polymer and plasticizer used in the extrusion process. Accurately weighed samples were maintained at 50°C for 1 minute and then heated to 600°C under nitrogen atmosphere (40mL/min at a heating rate of 10°C/min. The percentage weight loss was recorded with respect to temperature.

High Performance Liquid Chromatography

The chemical stability and content uniformity of the extrudates was confirmed using stability indicating RP-HPLC (Agilent Technologies 1200 Series). The system consisted of a UV detector, quaternary pump Chromatography was performed using a Zorbax Eclipse XDB-C 18 4.6 x 150mm 5µm column. The mobile phase, consisting of phosphate buffer pH 6.8 and acetonitrile in a ratio of 57:43 respectively, was eluted at a flow rate of 1 mL/min and the UV detector was set to a wavelength of 254 nm. 20 µL of sample was injected and chromatograms were monitored for drug content and any degradation peaks pre/post extrusion.

Differential Scanning Calorimetry

DSC measurements were carried out to monitor the extent of miscibility of RIF in the formulations using Pyris 6 DSC (Perkin Elmer). About 5-10 mg of sample was accurately weighed and hermetically sealed in an aluminum pan. The sample was equilibrated at 30°C for 2 minutes and was then ramped from 30 to 200°C at a heating rate of 10.0°C/min under a nitrogen purge of 20 mL/min.

Powder X-ray Diffraction (p-XRD)

Powder XRD patterns were acquired for the pure drug and formulations on X-ray diffractometer (Miniflex apparatus, Rigaku, Japan) using Cu Kα radiation at 25°C operated at voltage 45kV, current 20 mA, at a scanning speed of 1 min^{-1}.Data was recorded over an angular range from 2 to 50 (2θ scale) in continuous scan mode.

Fourier Transform Infrared Spectroscopy

A Perkin Elmer Spectrum RXFTIR (L1185247, Thermo Scientific, Mumbai, India) was employed to investigate the interaction of RIF with the polymer or plasticizer. The samples were pelletized with KBr and the pellet was analysed at scanning range of 450-4000 cm^{-1}. Change in characteristic peaks of the respective samples was recorded.

Scanning Electron Microscopy

Scanning electron microscopy was used to monitor the surface morphology of melt extrudates. The samples were mounted on an aluminum stage using adhesive carbon tape and were coated with platinum using a high vacuum evaporator. Scanning electron microphotographs were obtained using JEOL JSM-6380LA, Japan operating at an accelerating voltage of 15 kV.

Stability studies

The developed formulation were stored in HDPE containers and subjected to accelerated stability studies for six months at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH as per ICH guidelines and was monitored for drug content, release pattern and chemical stability.

RESULTS AND DISCUSSION

Oral drug delivery systems are the most preferred route of choice particularly for diseases like TB which requires long term treatment. In order to minimize the concerns associated with current TB therapy, controlled delivery systems providing long term therapeutic effect using a commercially viable technology like melt extrusion were resorted to. The developed formulation was designed to release RIF in two doses: loading dose of 300 mg as immediate release pellets and maintenance dose of 150 mg as melt extruded tablet.

Multiple unit particulate systems offers myriad of advantages over single unit systems. The formulation advantages include versatility of formulation design, convenient modulation of dosage strengths, tailoring release profiles at different site of GIT, delivery of incompatible drugs in a single dosage form, improved stability and ideal shape for application of film coating due to low surface to volume ratio (Sellasie, 1989; Melia et al., 1994). It also bears certain biopharmaceutical advantages like minimum risk of dose dumping, predictable, reproducible and short gastric residence time leading to less inter- and intra-subject variability,

enhanced bioavailability, reduced adverse effects and local irritation in the GIT, reduced food effects on drug absorption and improved patient compliance. In addition to this, there are regulatory advantages like extension of patent protection and product globalization (Roy and Shahiwala, 2009).

Pellets prepared using hot melt extrusion could be immediate release or controlled release depending on the type of matrix polymer used. Unlike the traditional pelletization techniques, number of processing steps are reduced, use of water or solvents are obviated, higher drug loading could be attempted, preliminary coating step is not necessary (Young et al., 2002).

Preformulation studies

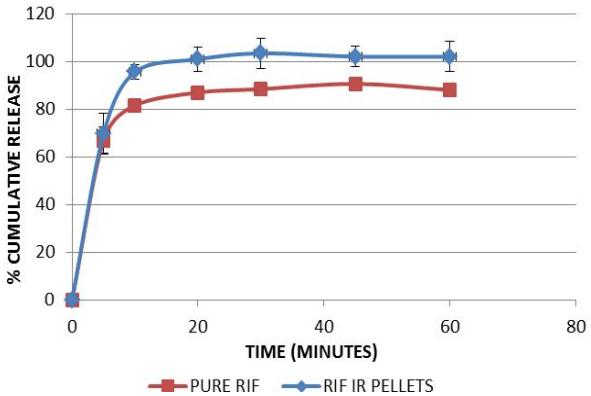
Preliminary investigations were carried out to determine the suitability of matrix polymers and plasticizers to be melt extruded with RIF. The physical mixtures of the same did not show any physical or chemical incompatibility (confirmed by DSC and IR studies) when stored at 40°C/75% RH for 15 days.

Selection of the matrix formers

Eudragit EPO, a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate was selected as the matrix former for immediate pellets due to its solubility in gastric fluid upto pH 5, excellent extrudability at moderate thermal conditions owing to its low glass transition temperature ~48°C and dimensional stability of the extrudates post extrusion (no die swelling). Triethylcitrate was added as the liquid plasticizer at 5% concentration since it is extremely miscible with Eudragit polymers and effectively reduced the Tg from 130°C to 110°C (Zhu et al., 2002). The flow characteristics of the polymer above their Tg depends on the melt viscosity which is controlled by the polymer molecular weight and molecular chain mobility. The frictional forces existing between polymer chains control the polymer chain diffusion and functional aids like plasticizers reduce these frictional forces thereby assisting in extrusion. The extrudates obtained exhibited no die swelling and good mechanical strength to withstand the pelletization process. For extended release tablets hydroxypropyl cellulose (HPC), a nonionic water soluble cellulose ether was explored as the matrix former. Selection of HPC was based on the preliminary trials conducted where it displayed ease of extrudability at lower temperature (i.e. 85°C-90°C), no die swelling owing to its low molecular weight (about 95,000), ability to accommodate higher drug loading (about 50-60%), high process yield (about 60-65% for a single screw extruder) due to the internal lubricants added to Klucel which ensure easy release from screw and barrel surfaces. Propylene glycol at 5% concentration was used as plasticizer to ensure smooth, uniform melt flow and homogenous end product.

***In vitro* dissolution studies**

In order to achieve the minimum effective concentration (MEC) of RIF and elicit the desired therapeutic effect in the body, IR pellets were designed to rapidly disintegrate and undergo complete dissolution. From the dissolution data (Figure 1), it is evident that IR pellets of RIF underwent complete dissolution in 10 minutes whereas pure RIF showed an incomplete release till the end of an hour. Enhanced dissolution rate displayed by pellets could be attributed to interaction of cationic Eudragit EPO with phenolic hydroxyl groups of RIF resulting in a complex having higher dissolution at gastric pH. The plateau effect shown by pure RIF powder could be due to electrostatic charges causing aggregate formation thereby reducing the surface area of the drug exposed to the dissolution medium.



**Data is expressed as mean ± SD, n = 6*

Fig. 1: Dissolution of immediate release (IR) pellets of Rifampicin.

The formulation containing medium viscosity grade of HPC (Klucel MF, Pharm) RFX-H1 could release only 40% RIF at the end of 24 hours whereas lower viscosity grade (Klucel LF, Pharm) RFX-H2 extended the release upto 17 hours (Figure 2). The difference in release from both the matrices was due to the difference in their solubilities in the dissolution medium and length of their swollen phases. Thus, it was thought that a combination of both viscosity grades (RFX-H3) could optimally control the release rate. The burst release from Klucel LF matrix was reduced by addition of 30% (of base polymer weight) of Klucel MF thereby extending release upto 24 hours (Figure 2). Swelling and erosion tendency of the hydrated matrix was reduced due to the presence of the poorly soluble RIF particles within the matrix. Hence, RIF release was primarily due to matrix erosion, which occurred at a constant rate resulting in zero order release (Table 1).

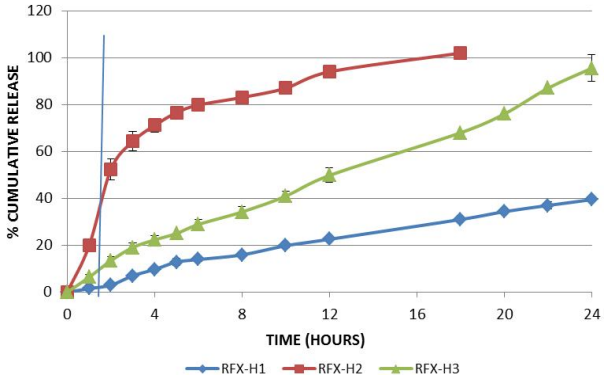


Fig. 2: Dissolution of extended release melt extruded tablets of Rifampicin: RFX-H1: Klucel MF, RFX-H2: Klucel LF and RFX-H3: Klucel LF (70%) + Klucel MF (30%)

Table. 1: Drug release kinetics of the optimized batch (RFX-H3)

Release kinetics	Correlation coefficient (r^2)
Zero order kinetics	0.995
First order kinetics	0.862
Higuchi release	0.968
Korsmeyer Peppas	0.961

Characterization of the developed formulation

The formulation was characterized with respect to thermal and chemical stability, miscibility, drug–polymer interaction and surface morphology as follows:

Thermogravimetric analysis

Thermogravimetric analysis was carried out as a preliminary check on the thermal stability of the polymers and drug employed. There was no weight loss recorded for RIF upto 195.58°C (Figure 3a) indicating absence of either solvate or hydrate in the sample.

It did not reveal any signs of degradation at the processing temperature thus confirming stability during the residence time of about 3 minutes while extrusion. Similarly, HPC did not show any signs of degradation at the processing temperature (Figure 3b).

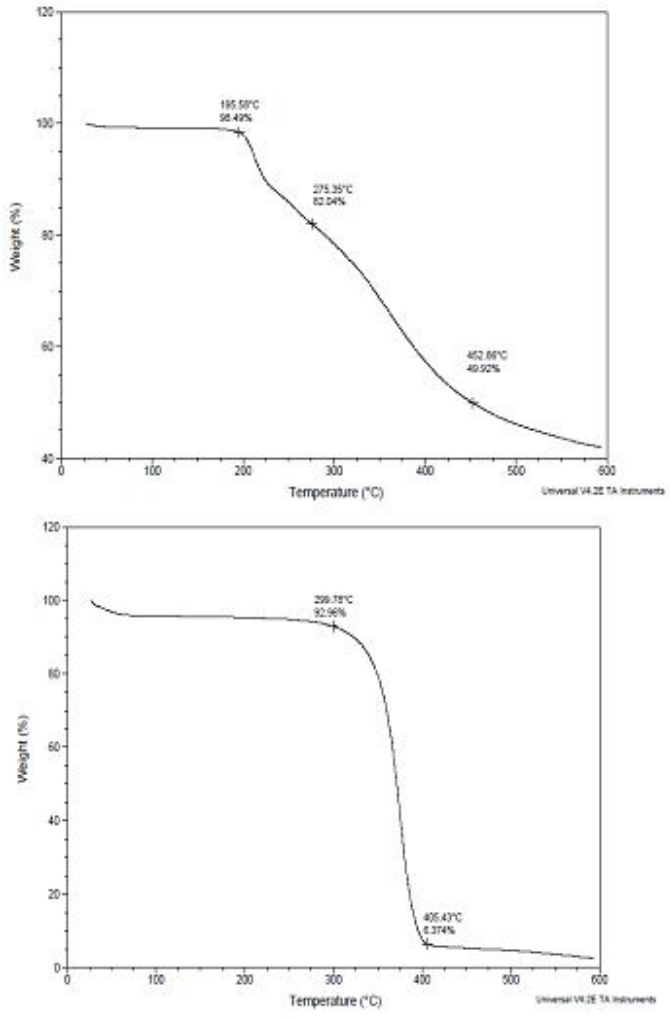


Fig. 3: Thermograms of a. Pure Rifampicin b. Pure Hydroxypropyl cellulose.

High Performance Liquid Chromatography

HPLC chromatograms of the pellet and tablet formulation before and after extrusion did not show any degradant peaks or any significant change in the shape, height or retention time of the characteristic RIF peak there by confirming its chemical stability (Figure 4).

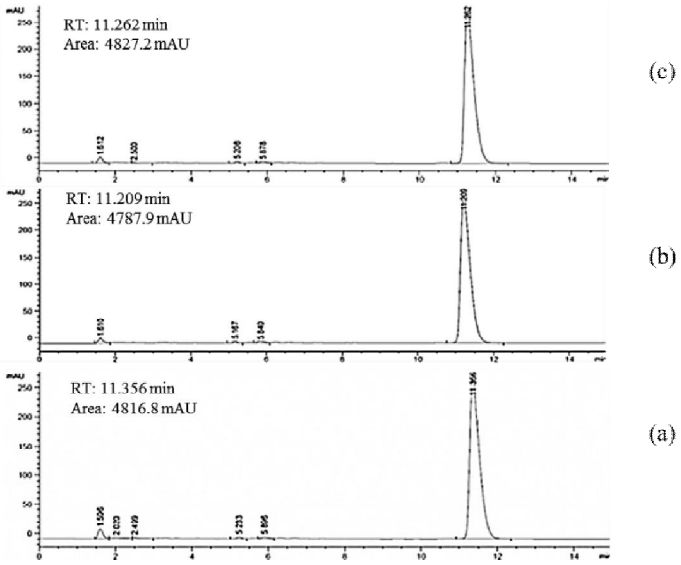


Fig. 4: HPLC Chromatograms of (a) Pure Rifampicin (before extrusion) (b) RIF IR pellets and (c) RIF ER tablets.

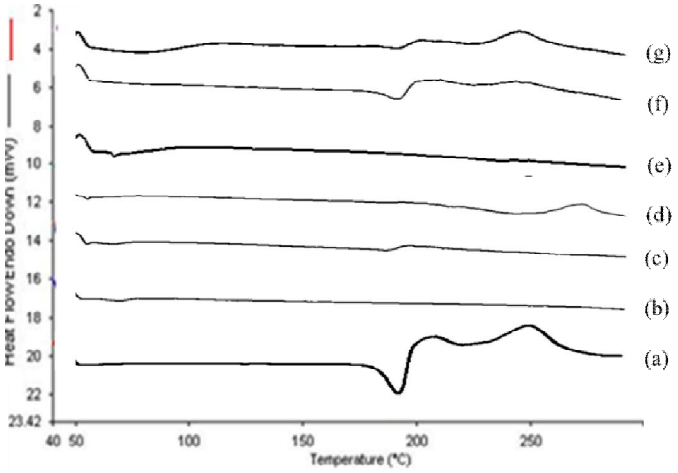


Fig. 5: DSC thermograms of a. Pure Rifampicin b. Plain Eudragit EPO c. Physical mixture of RIF and Eudragit EPO d. RIF IR pellets e. Plain Klucel f. Physical mixture of RIF and Klucel and g. RIF ER tablets.

Differential Scanning Calorimetry

The DSC curve of pure RIF (Figure 5a) exhibited distinct melting endothermic peak at 193.69°C, followed by crystal transformation to form I between 199.96–213.98°C, which is a characteristic of solid-liquid-solid transition and decomposition of form I in the range of 232–265°C. This melting behavior is typically followed by Rifampicin metastable polymorph form II (Freire, 2009). Thus, in addition to thermal stability and miscibility, DSC measurements could also reveal changes in the

polymorphic forms of RIF on extrusion. Thermograms of plain polymers showed absence of Tg owing to their amorphous nature. Fig. 5c and 5f depicts thermograms of physical mixtures of RIF with Eudragit EPO and Klucel with the characteristic endothermic peaks of RIF. In case of IR pellets, Eudragit EPO had successfully solubilized RIF indicated by absence of RIF endothermic peak (Figure 5d). On the other hand, Klucel was capable of effectively dispersing RIF (partial solubilization) forming a solid dispersion indicated by a small endotherm (Figure 5g). Additionally, DSC data also suggested partial conversion of the crystalline to amorphous forms which was further confirmed by p-XRD studies.

Powder *X-ray diffraction*

The characteristic peaks of pure RIF form II are depicted in Figure 6a at 9.96 and 11.1° respectively. The peaks in melt extruded pellets and tablets appeared to be less intensive with decreased sharpness of diffraction patterns compared to pure RIF inferring partial drug solubilisation within the polymeric matrix. These observations further confirm the findings of DSC of partial conversion of crystalline to amorphous form.

Fourier transform infrared spectroscopy

In RIF, all the functional groups that can be involved in H-bonding are bonded intramolecularly that shows differences in ansa OH, furanonic, acetyl and amide C=O frequencies. The possible intramolecular bonding reported in the IR spectrum of rifampicin in CDCl3 solution are C21 hydroxyl is H-bonded to the C23 hydroxyl which in turn is H-bonded to C25 acetyl, C8 hydroxyl is bonded to C1 hydroxyl which in turn is bonded to the amide carbonyl, C4 hydroxyl is bonded to furanone carbonyl and the amide NH to imine nitrogen of the substituent at C3 (Pelizza, 1977).

In form II, C4 hydroxyl is not bonded to furanone carbonyl and C1 hydroxyl is not bonded to amide carbonyl. FTIR spectra of form II RIF exhibited a distinct double peak at 1723 and 1718 cm−1, broad band over 3560–3100 cm−1 due to absorption by ansa OH group (Figure 7a).

The characteristic double peak of RIF was retained at 1720-1723 cm-1in both the pellet and tablet formulation confirming the chemical stability (Figure 7d and 7e). The characteristic peaks of Eudragit EPO at 1594, 1730 and 2955 cm-1 were quite evident in the spectra of RIF pellets. Similarly, the typical peaks of Klucel at 1595 and double peaks at 2922 and 2980 cm-1 were quite distinct in the spectra of RIF tablet. Moreover, there was broadening of the peaks signifying possibilities of hydrogen bonding between the drug and polymer.

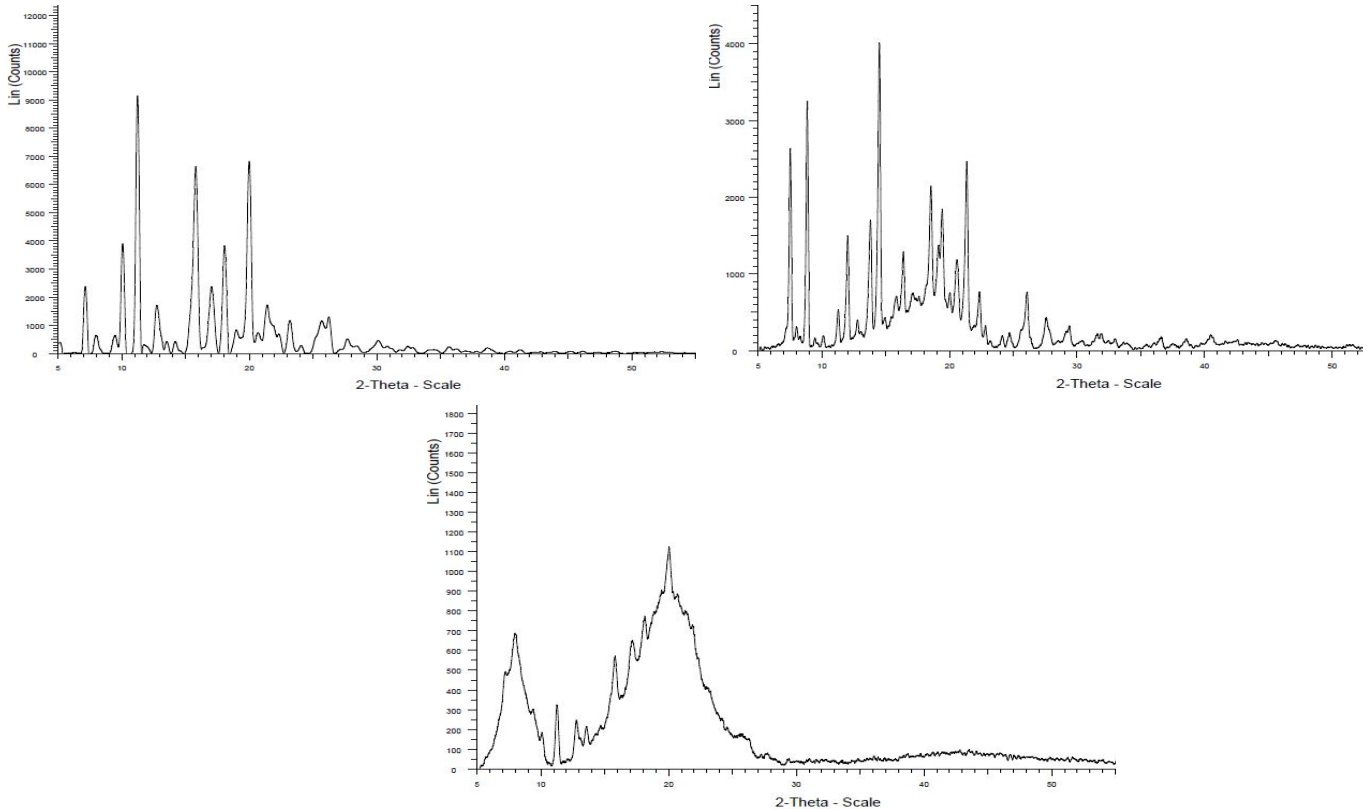


Fig. 6: X-ray diffractograms of a. Pure Rifampicin b. RIF IR pellets and c. RIF ER tablets.

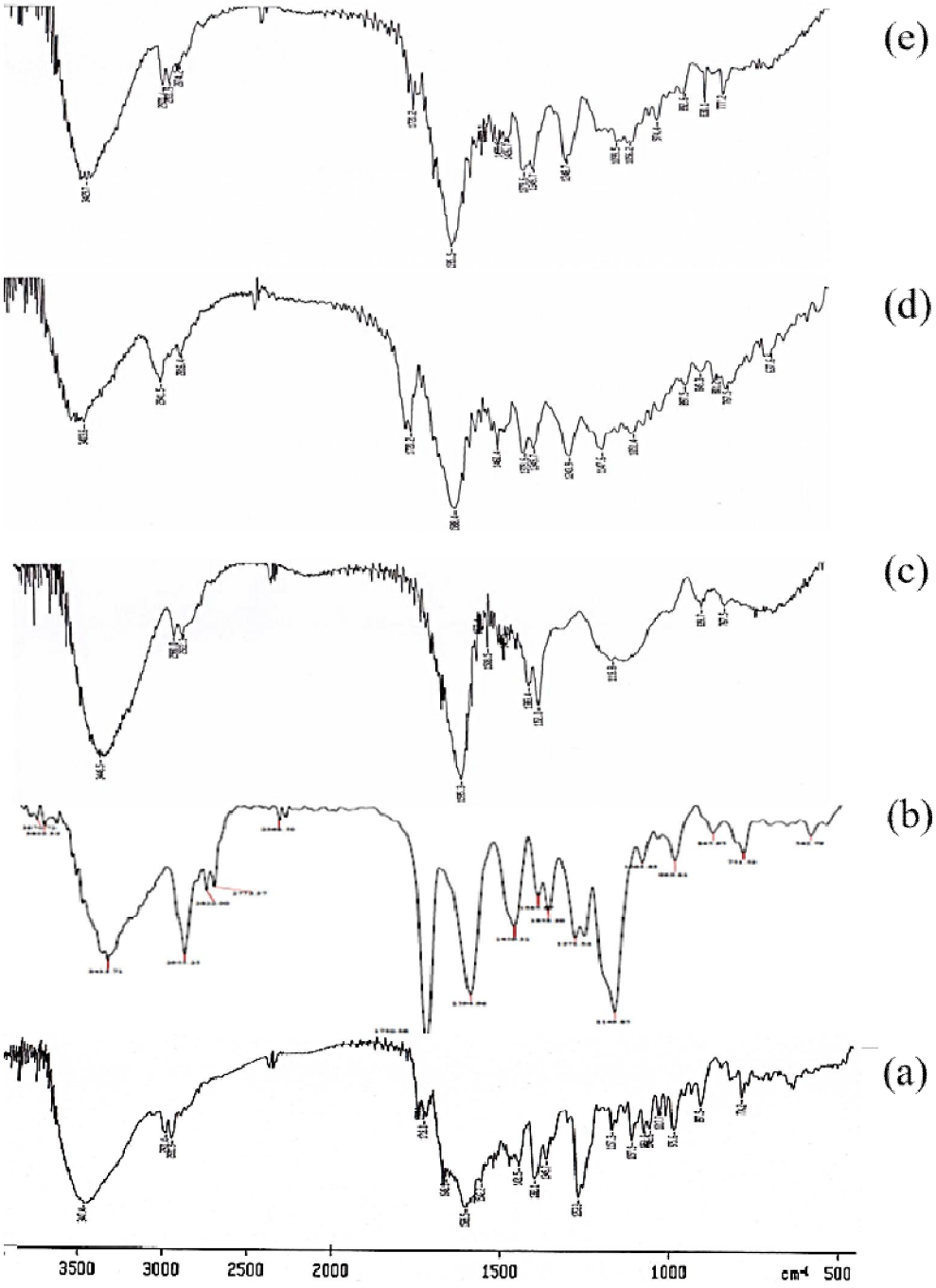


Fig. 7: Infrared spectras of a. Pure Rifampicin b. Plain Eudragit EPO c. Plain Klucel d. RIF IR pellets e. RIF ER tablets.

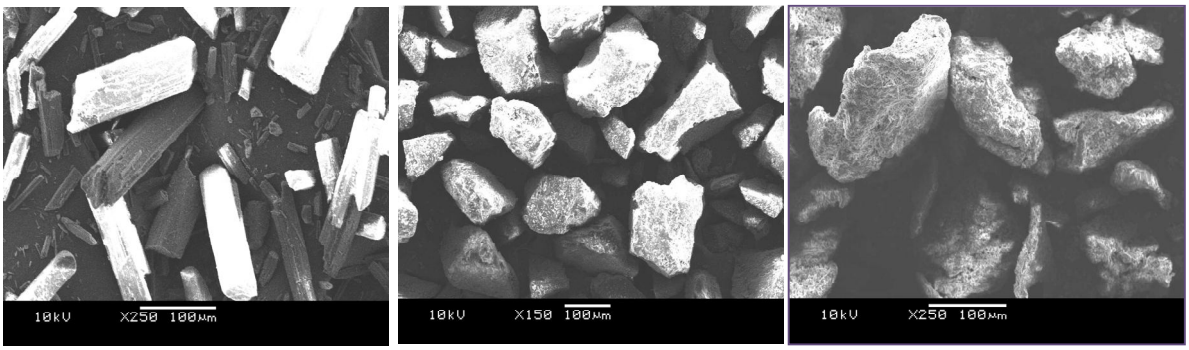


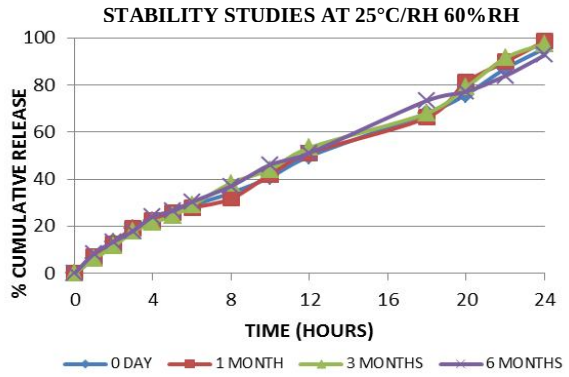
Fig. 8: Scanning electron micrographs of a. Pure Rifampicin b. RIF IR pellets (powdered) and c. RIF ER tablets (powdered).

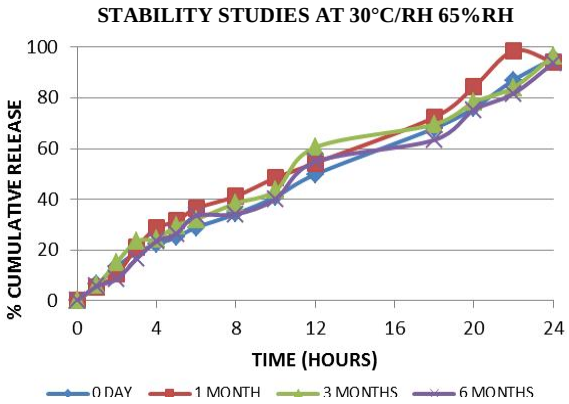
Scanning Electron Microscopy

Figure 8 represents the changes in surface morphology of RIF after extrusion. Pure RIF was seen as uniform rod like particles. The melt extruded pellet and tablet formulation (powdered) exhibited a continuous single phase devoid of long range crystal lattice indicating homogenous molecular level dispersion of RIF in the continuous polymeric structure.

Stability Studies

The developed formulations were found to be stable at the end of six months with no significant change in drug content (Table 2) and dissolution behavior (Figure 9) at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH respectively.





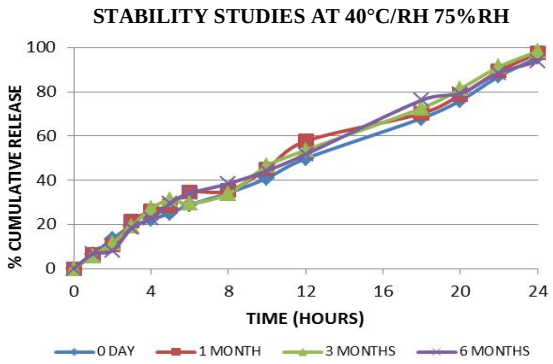


Fig. 9: Effect of storage on dissolution behavior of Rifampicin ER tablets at a. 25°C/60% RH b. 25°C/65% RH and c. 40°C/75% RH

CONCLUSION

An extended release system providing controlled delivery of RIF at a zero order rate was successfully developed using hot melt extrusion technique. A simple combination of pH independent hydrophilic swellable polymers like hydroxypropyl cellulose can be utilized to fabricate an extended release matrix. It was found to be thermally and chemically stable. Melt extrusion proved to be well suited for the classical molecule Rifampicin which is known to possess pH dependent degradation, variable bioavailability and GMP concerns. This industrially feasible, cost effective technology which has never been explored earlier for anti-TB formulations could be a valuable contribution towards management of TB till more potent drugs become available.

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