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SF/Poly(Ethylene-Co-Vinyl Acetate) Blends For Controlled Drug Release

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Abstract: Silk fibroin (SF)/poly (ethylene-co-vinyl acetate) (EVA) blends were prepared in different blend ratios and the properties were studied with respect to blend ratios. X-ray diffraction (XRD) and Fourier transformation infrared spectroscopy (FTIR) of the blends were carried out to determine the blend mixing and the state of drug in the blends. FTIR and XRD results showed good compatibility in the blend system. The swelling ratio of the blends were found to be increasing with decrease of EVA content. The degradation study showed that the percentage of mass remaining increases with increase in amount of EVA. The drug release profile showed a varying trend with amorphous nature of SF and semicrystalline behavior of EVA. The studies of the present system indicated that the drug release from the present blend system can be manipulated as per the requirement by controlling the blend ratios.
Keywords: SF, Ethylene-vinyl acetate, Ciprofloxacin, Drug delivery system.

Introduction

The concept of controlled release is a novel approach to the safe and effective use of any active ingredient, whether antibiotic, drug or herbals. In a controlled release formulation, the active ingredient is released at a continuous and constant rate of a predetermined period. Several technologies have been developed to control the release rate of particular drugs. One of the techniques that can potentially control the rate of drug release is the formation of a matrix with a polymer. The use of drugs dispersed in an inert polymer to achieve the controlled release through diffusion has attracted considerable attention[1-4]

Polymeric-based Control delivery systems can be prepared in numerous different ways. Dispersing a drug, or therapeutic agent, in biocompatible and/or biodegradable polymeric matrices encompasses the majority of all research in this field. The aim of the present work was to prepare SF (SF)/ poly(ethylene-co-vinyl acetate) EVA blends of different ratios and study their morphology and drug release profile. The blends were prepared by solution casting. The work also intended to study the drug release profile of the blend system with varying morphology of the blend ratios. The dispersion of the drug in the blend system and the stability, swelling behavior and sol fraction of the blend were also analyzed at different blend ratios.

SF is an interesting polymer used for drug delivery of polysaccharides and bioactive proteins due to its ability to process the biomaterials in biocompatible fashion under ambient conditions [5-6].One of the sources for SF is Bombyx mori silk worm. Bombyx mori silk, a member of Bombycidae family is composed of a filament core protein, fibroin, and family of sericin proteins which act as glue to bind two fibroin filaments together [7-11]. SF is non-toxic to human because it is similar to amino acids in human. Ethylene vinyl

acetate (also known as EVA) is the copolymer of ethylene and vinyl acetate. It has been widely used as a membrane or matrix for transdermal drug delivery systems [12-16]. Ciproflaxin was chosen as a model drug due to its broad spectrum activity as well as for the presence of reactive amine and carboxylic acid functional group. This antibiotic is the leader among the third generation fluroquinolones with a broad spectrum of antibacterial activity.

Materials and methods

SF from Bombyx mori silk was obtained from central silk board at Bangalore. EVA with 18% vinyl acetate is from Dupont. All other chemicals were of reagent grade. B. mori silk cocoons were cut into small pieces and degummed by boiling twice; 20 min each, in an aqueous solution of 0.02 M Na_2CO_3 in order to remove silk sericin [17]. The product obtained is dissolved in 1:9 solution of calcium chloride and formic acid by stirring. This is followed by dialysis against distilled water for three days at room temperature using cellulose dialysis membrane (MWCO 12 kDa) with frequent water changes. The SF and EVA were mixed in different ratios (0/4, 1/3, 2/2, 3/1, 4/0 of SF and EVA respectively). Fixed amount of drug was added to these blend ratios during the blending.

Swelling properties were studied using conventional gravimetric procedure (Biman B. Mandal). In vitro degradation of blends were investigated by monitoring loss of weight in water having pH 2. The samples were prepared and initial dry mass of all formulations was noted down. Each of the blends was immersed in 50 ml of water. After 24 hr the samples were removed from the medium and dried at room temperature. The % mass remaining was calculated using the formula

% mass remaining = (mass at time t/ initial mass) X 100

The drug release studies were conducted at a Ph 2. FTIR spectra are obtained from the test systems using potassium bromide disc method using THERMO NICOLET AVATAR 330 FTIR spectrophotometer. XRD patterns were measured using BRUKER (Germany D8 Advance) X- ray diffractometer.

Results and discussion

The swelling ratios of the blends and the individual polymers alone are given in **Fig 1. Fig. 2 sho**ws the swelling properties of the same components after drug incorporation. Swelling ratios were found to be dependent on blend composition. At any given time, the swelling ratio of EVA is found to be much lesser than SF. However the swelling ratio of silkfibroin drastically decreased with an increase in EVA incorporation. This may be due to a higher crosslink density and semi-crystalline nature of EVA matrix. At lower crosslink density, the network was loose and has a high free volume to accommodate more of the solvent molecules, thereby increasing matrix swelling. Intense crosslinking and crystallinity hinders mobility of water, hence lowering the swelling ratio and equilibrium water content. The swelling ratio of the polymers alone as well as the blends were found to decrease after the incorporation of drug. The EVA system showed a much lesser swelling property than SF. However the blends showed an intermediate swelling. The slight increase in swelling on incorporation of drug may be due to the dissolution of water soluble drug. Once the drug gets dissolved, larger voids are left in the polymers and the water imbibing becomes much easier. Also the diffusion and transport becomes much easier in the loosely held polymers.

In-vitro degradation of the individual polymers and its blend system are given **in Table 1**. Degradation was found to be higher for SF while EVA showed negligible degradation. The blend system showed an intermediate value, or the degradation of SF reduced on the incorporation of EVA. One of the reasons may be the hydrophobic nature of EVA. Also, increase in EVA content resulted in denser networks which lowered the diffusion of water within the networks. This resulted in increased resistance against hydrolysis and degradation. The lowering of the degradation or the swelling ratio also indicates a good blending of the two polymer systems.

Table 1. In-vitro degradation of SF/EVA blend system

Blend ratio	(% mass remaining)
0/2	99.1
2/2	85.6
2/0	79.86

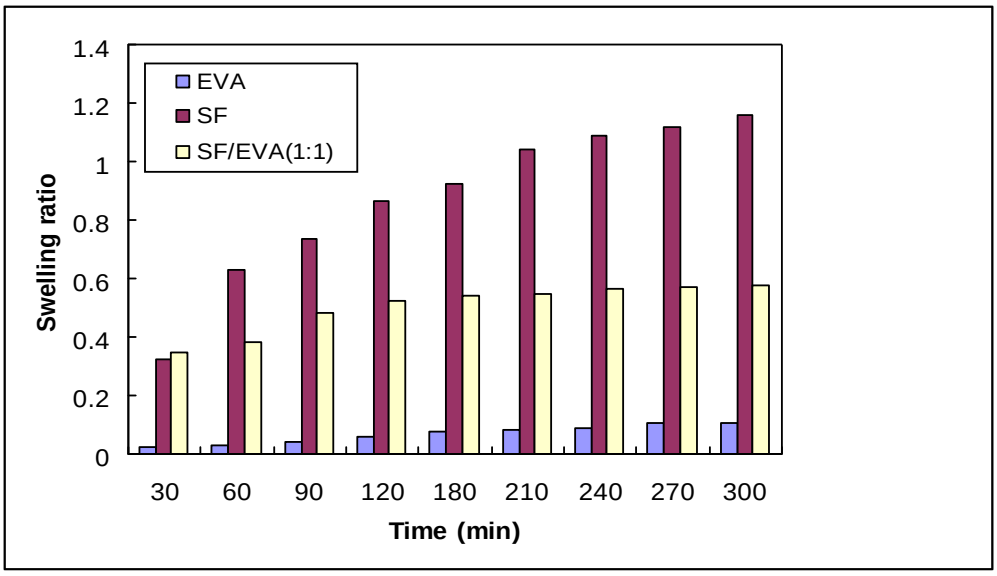


Fig 1. Swelling ratio of silk fibroin/EVA blend without drug

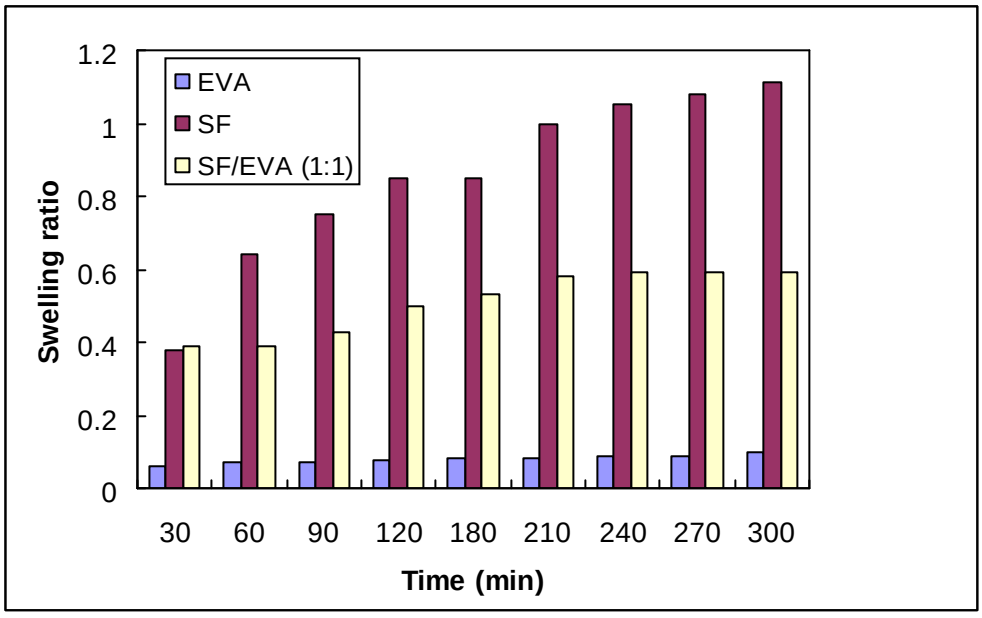


Fig 2. Swelling ratio of silk fibroin/EVA blend with drug

Fig. 3 (a– e) shows the drug release profile of various blend systems. The release of drug was evaluated as a function of composition of SF and EVA. The blends displayed different release profiles depending on their composition. The blend having more amount of SF showed maximum release when compared to other blends. At the same time EVA alone showed a very low percentage of drug release. As the percentage of SF increased in the blend, its drug release also increased. From this it can be understood that the release rate by SF can be controlled by incorporating EVA. Release of drug from blend is governed by several factors such as nature and molecular weight of the drug, degree of crosslinking density and pore size of polymer, solvent type etc. The release of the drug molecules into the solution may be occurring in two ways – the polymer networks get loosened on exposure to the solution and the drug molecules gets larger path way to move and come out of the polymer system and enter the solution. Secondly the solution molecules diffusing through the polymer network reach the drug molecules and dissolve the drug and makes the release faster. In either of the case – diffusion of the solution molecules into the polymer matrix or the drug molecules diffusing in to the solution through the polymer networks- the

rate depends totally on how the polymer interacts with the solution. Since the solution used here is made up of water, the hydrophobic and semicrystalline EVA having a highly crosslinked structure shows very less loosening of the net work. This results in lowering of the molecules through the polymer network. This factor is also supported by the above observations in the case of swelling properties and in vitro degradation. However it becomes much easier for the solvent as well as the drug molecules to move through the amorphous SF. This indicates that the release profile of the blend system can be tuned to requirement by varying the blend ratios.

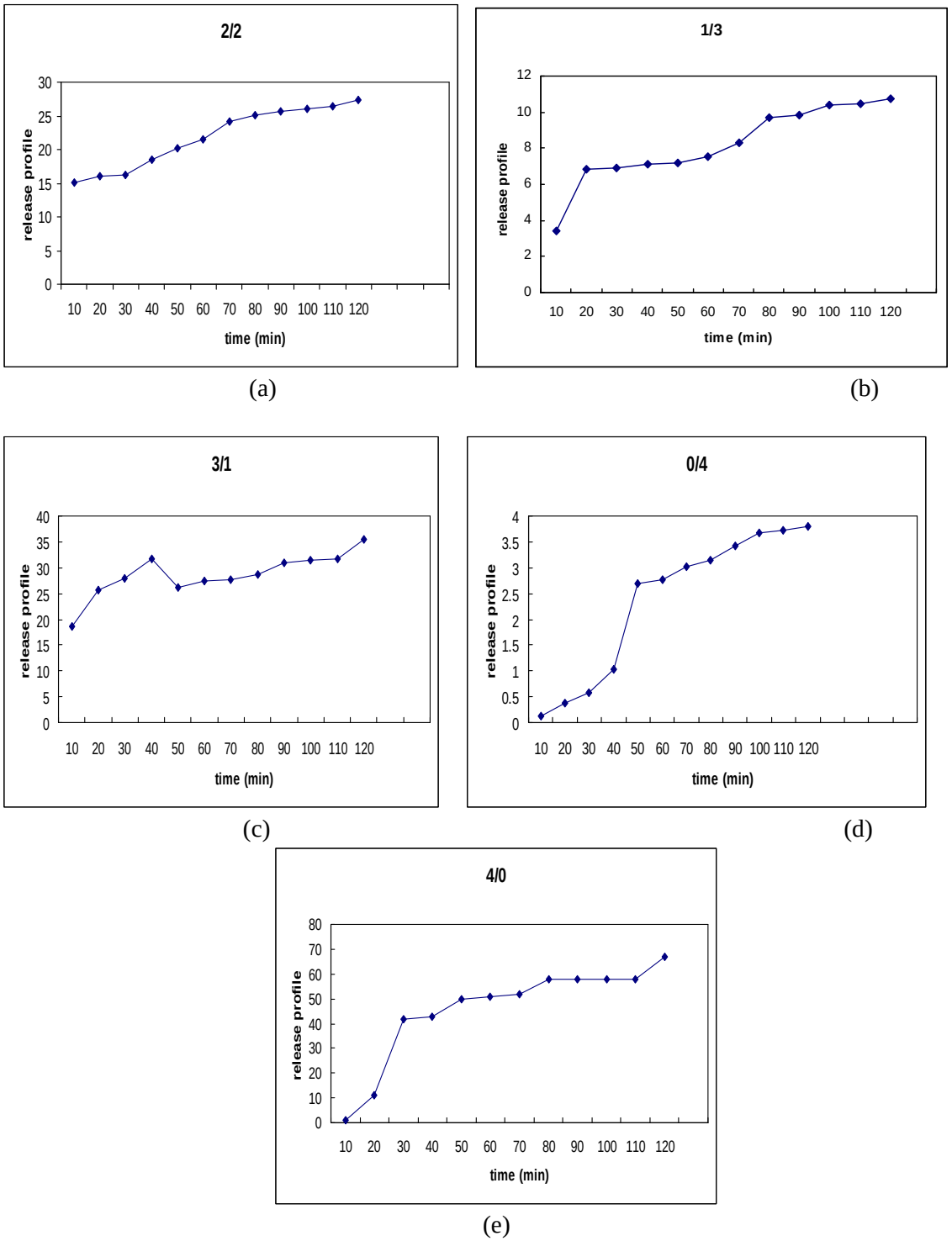


Fig. 3 (a-e). Release profile of (a) 2/2 (b) 1/3 (c) 3/1 (d) 0/4 (e) 4/0 ratios of SF/EVA blends loaded with drug.

XRD pattern of **SF (Fig. 4) showed** no diffraction peaks indicating that SF is present as an amorphous form. Meanwhile the XRD of EVA showed sharp crystalline peaks. The XRD of the SF/**EVA (Fig. 5) blend showed** lesser crystalline peak indicating a semi amorphous phase. This shows a good compatibility of the blend and that the amorphous nature of the blend can be varied by varying the blend ratios. The same trend is observed for the blend incorporated with ciproflaxin **(Fig 6). The blend showed** a good miscibility of the polymers and it indicates that ciproflaxin does not interfere in the compatibility of the blends. The XRD of the **ciproflaxin (Fig. 7)** showed high crystallinity which is missing in the XRD of the blend with ciproflaxin. This indicates physicochemical interactions between ciproflaxin and SF/EVA matrix, might occur at the molecular level, and that ciproflaxin was not crystalline in the SF/EVA matrix.

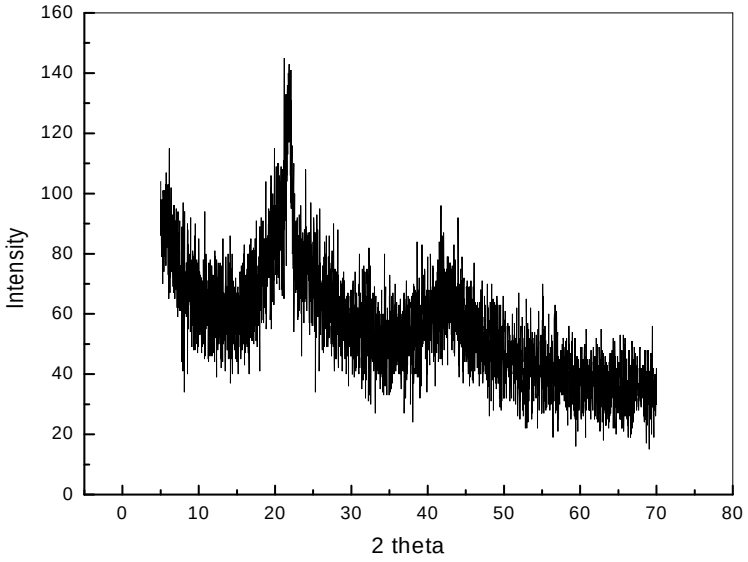


Fig. 4. XRD of silk fibroin

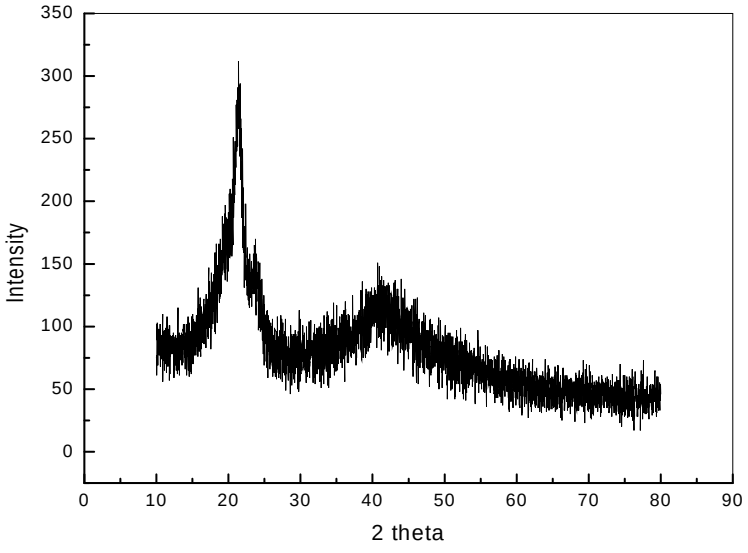


Fig. 5. XRD of SF/EVA blend system

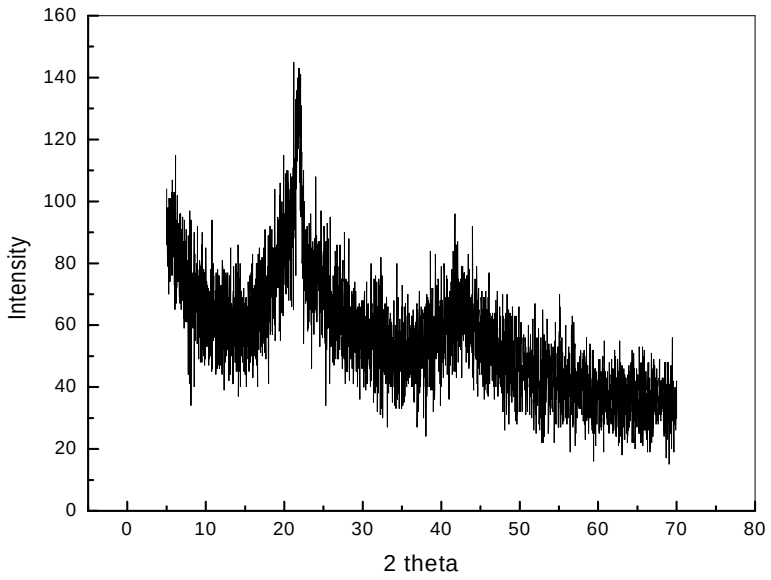


Fig. 6 XRD of SF/EVA blend incorporated with drug

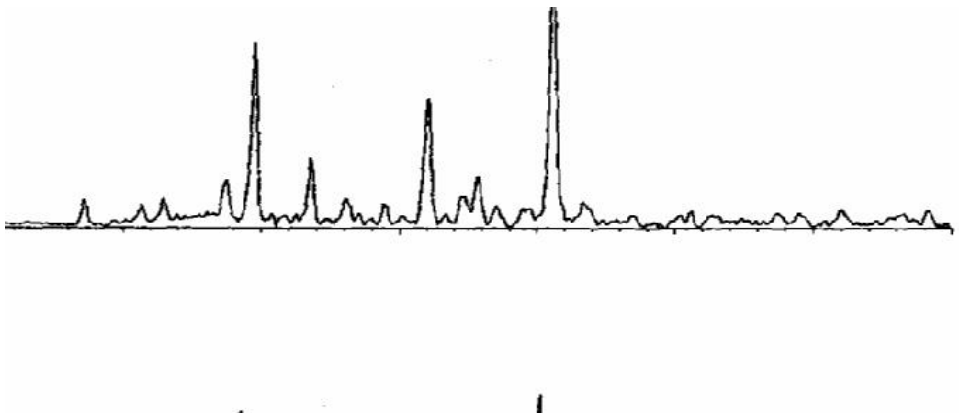
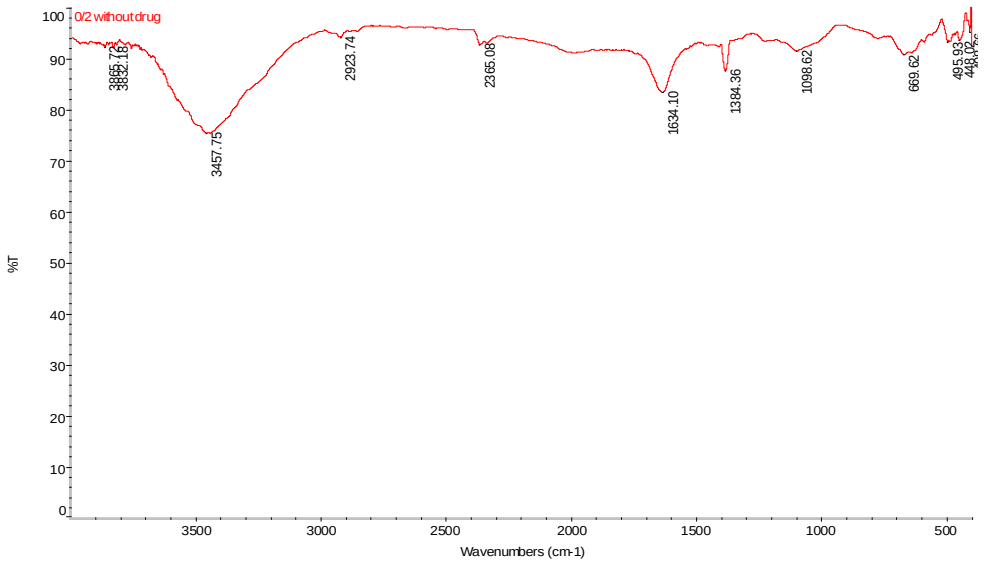


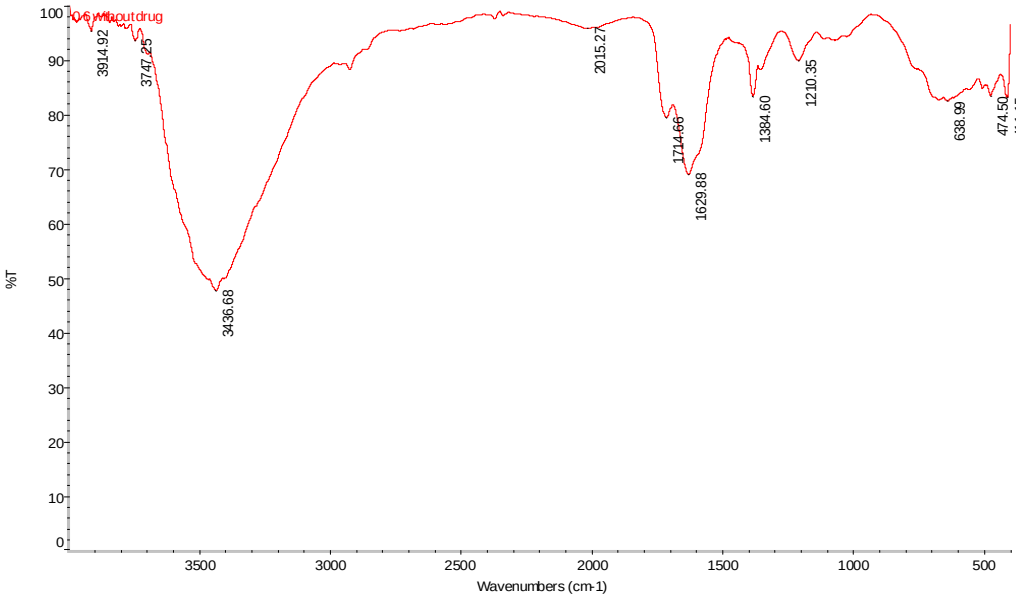
Fig. 7 XRD of SF/EVA blends system

The representative FTIR spectra of SF and the blends with different compositions are shown **in Fig.8 (a –g).** The spectrum of untreated SF shows typical peaks at 1629, 1384, 1210 cm^{-1}, assigned respectively, to amide-I (C=0 stretching), amide-II (NH deformation and C-N stretching) and amide-III (C-N stretching and N-H deformation) bands of a random coil conformation. The absorption of band around 2923 cm^{-1} of –CH stretching vibration illustrating the presence of EVA. The spectrum of ciproflaxin shows an absorption band around 1627.1 cm^{-1}. A peak close to 1635.4 in the spectrum of various blends was due to participation of either ketone or carboxylic group. The intensities of peaks decreased proportionally, with an increasing amount of EVA. The spectrum of blends with drug does not show the absorption band around 2923 cm^{-1} of EVA. It was presumably suggest that ciproflaxin was dispersed at the molecular level. This suggests that ciproflaxin is present in the SF and EVA blend as an amorphous form.

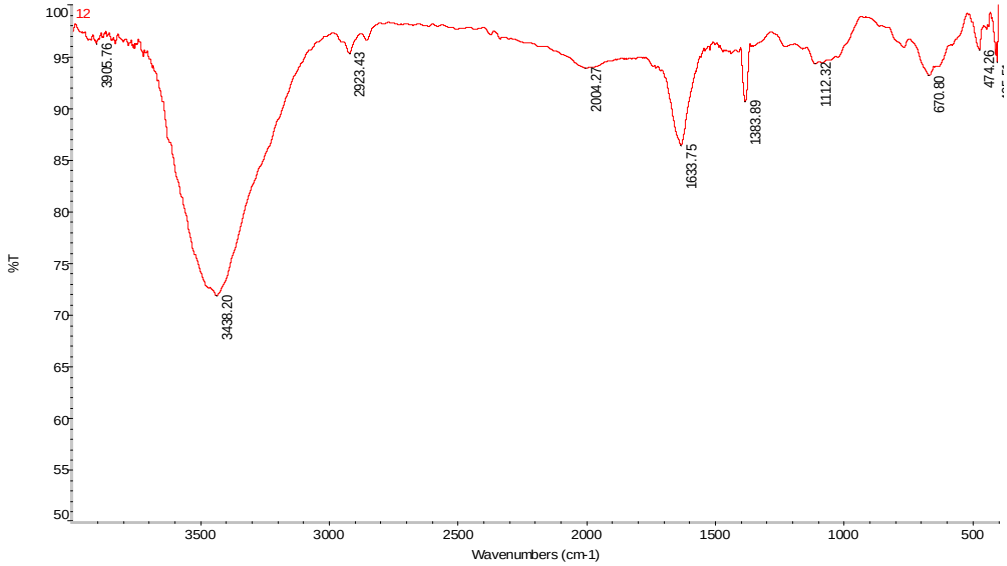
Fig 8.


0/2 without drug
3457.75
2923.74
2365.08
1634.10
1384.36
1098.62
669.62
%T
Wavenumbers (cm-1)

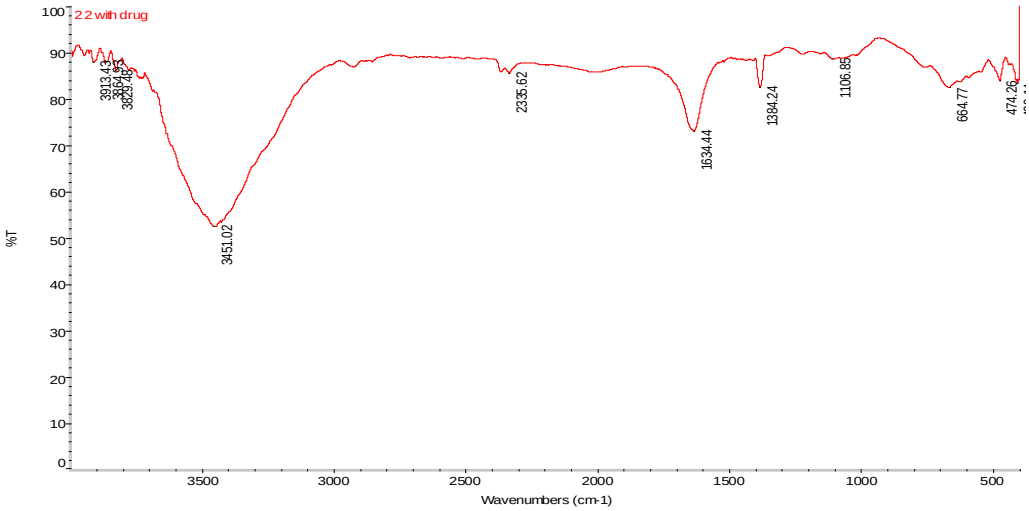
(a)


3914.92
3747.25
3436.68
2015.27
1714.66
1629.88
1384.60
1210.35
638.99
474.50
%T
Wavenumbers (cm-1)

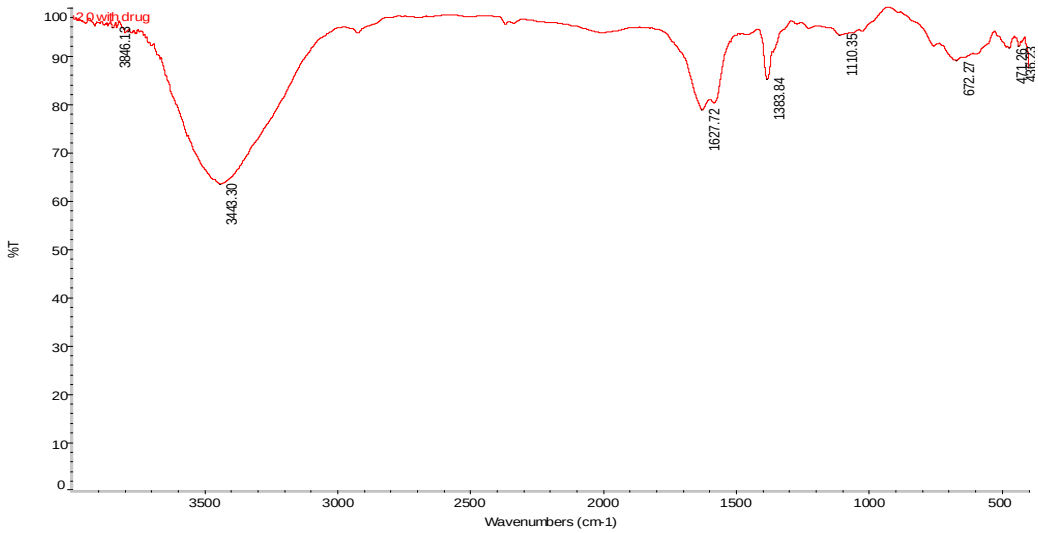
(b)


12
3905.76
3438.20
2923.43
2004.27
1633.75
1383.89
1112.32
670.80
474.26
%T
Wavenumbers (cm-1)

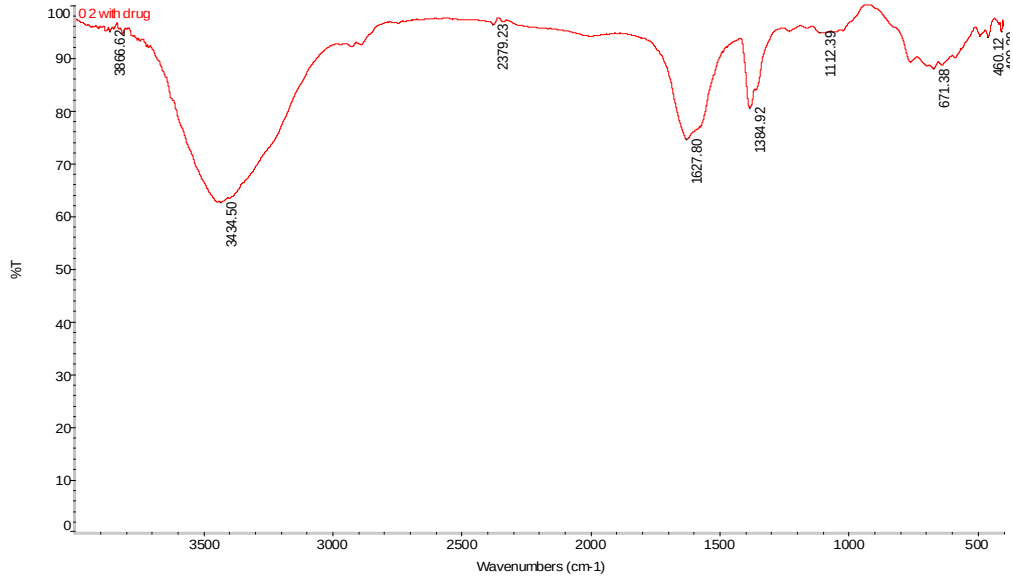
(c)


2 2 with drug
3913.43
3829.48
3451.02
2335.62
1634.44
1384.24
1106.85
664.77
474.26
%T
Wavenumbers (cm-1)

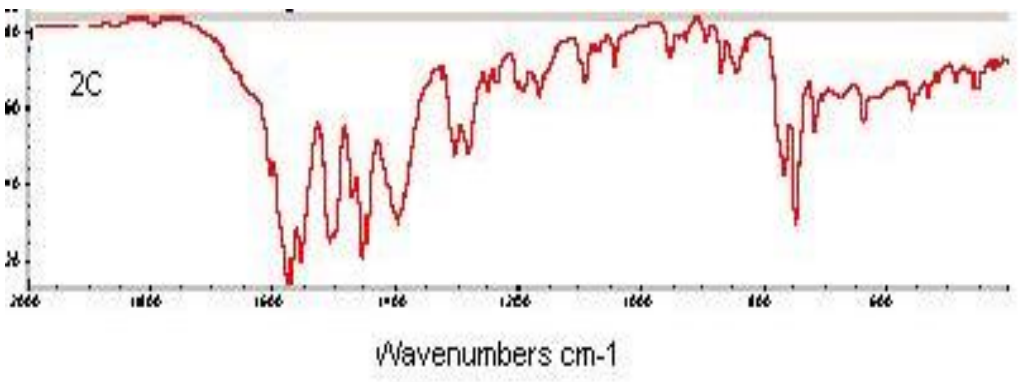
(d)



(e)



(f)



(g)

Fig 8. Showing FTIR spectra of (a) 0/2 (b) 2/0 (c) 1/1 SF/EVA blends without drugs. (d) 1/1 (e) 2/0 (f) 0/2 of SF/EVA blends with drug, (g) ciproflaxin

Acknowledgements

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