

Effect of hydrophilic and hydrophobic polymers and fillers on controlled release matrix tablets of acyclovir

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ABSTRACT

Acyclovir was formulated as oral controlled release matrix tablets using hydrophilic and hydrophobic polymers separately or in combinations. Tablets were prepared by direct compression method. The tablets were evaluated to thickness, weight variation test, drug content, hardness, friability and in vitro release studies. All the formulations showed compliance with pharmacopoeial standards. The tablets prepared with triple combination of ethyl cellulose, eudragit RSPO and eudragit RLPO failed to produce the desired controlled release. The results of dissolution studies indicated that formulation F2 was most successful of the study. The formulation F2 exhibited Anomalous (non-Fickian) diffusion mechanism. Based on the results of in-vitro studies it was concluded that the hydrophilic and hydrophobic polymers can be used as an effective matrix former to provide controlled release of acyclovir. SEM images of tablet after dissolution showed pore formation. No interaction between acyclovir and excipients were observed from FT-IR and DSC studies

Key words: Acyclovir, Hydroxy propyl methylcellulose (HPMC K100), Ethyl cellulose (EC), Eudragit RSPO, Eudragit RLPO.

INTRODUCTION

Oral route of drug administration is oldest and safest mode of drug administration. It possesses several advantages. It does not pose the sterility problem and minimal risk of damage at the site of administration. Most commonly used method of modulating the drug release is to include it in a matrix system because of their flexibility, cost effectiveness and broad regulatory acceptance.

In order to enhance the patient compliance, get better clinical efficacy of drugs having short half life, keep uniform drug levels, trim down dose, side effects and to deliver drugs at programmed rate, controlled release formulations have been developed¹. Several polymers are used in the formulation of controlled drug delivery system.

Use of hydrophilic and hydrophobic polymers in matrix for controlled release of an active agent is known in the art. Hydroxy propyl methylcellulose is the dominant hydrophilic vehicle for the preparation of oral controlled drug delivery systems. Numerous studies have been reported in literature review^{2,3}. For preparation matrix tablets containing both soluble and poorly soluble drugs ethyl cellulose has been broadly used⁴. By varying of the combination and concentration of hydrophilic, hydrophobic component such as ethyl cellulose, HPMC k100 controlled release of drug are able to be obtained. HPMC K100 and ethyl cellulose has different swellable and permeable nature, blend of these two can alter the drug release rate. Therefore both were considered for combination⁵. In order to get pH independent delayed release of drug, compressible and swellable pH independent polymers of eudragit RLPO and eudragit RSPO were used. They were developed and suggested for preparing sustained release dosage forms⁶. By using direct compression method controlled drug delivery system could be developed. Acyclovir is a potent antiviral drug useful in the treatment of Herpes simplex, Herpes zoster,

Chicken pox and HIV infection. Acyclovir has a short biological half life 2.5h and also dosing frequency of 200mg/400mg 5 times a day depending upon type of infection. An alternative dose of 800mg leads to plasma fluctuations. Controlled release formulation is need for acyclovir because of it short biological half life and also to overcome adverse side effects, poor patient compliance, reduce dose and maintain uniform drug levels⁷.The objective of present work is to develop a controlled release matrix tablets of acyclovir by using different hydrophilic and hydrophobic matrix polymers alone or in combination and to study the effect of polymer combination and concentration on release pattern.

MATERIALS AND METHODS

Acyclovir is obtained as gift sample from Arochem Industries (Mumbai). HPMC K 100, ethyl cellulose, eudragit RLPO and eudragit RSPO were purchased from Research lab Fine Chem Industries (Mumbai), Micro crystalline cellulose was procured from Loba Chem PVT .LTD, (Mumbai). Magnesium stearate, Lactose and Talc was obtained from Sd Fine Chem LTD (Mumbai). Starch 1500 was a gift from Strides Arcolab, Bangalore. All the other ingredients used throughout the study were of analytical grade and were used as received.

Fourier transform infrared (FT-IR)Studies:

FT-IR spectra of pure acyclovir and their respective physical mixture were taken to assure the compatibility between pure acyclovir and its physical mixtures. Infrared spectrum was taken (Shimadzu FT-IR system,Japan) by scanning the sample in KBr discs .

Differential scanning calorimetry (DSC) studies:

To investigate the interactions of acyclovir with polymers and different excipients , DSC studies were also conducted. It was carried out with a differential scanning calorimeter (DSC, Perkin-Elmer; Pyris-1).

Preparation of matrix tablets:

Matrix tablets were prepared by direct compression method. The composition of various formulations is given in Table 1 . All the ingredients were sieved by mesh (no.40) and mixed with other ingredients and the powder mixture was compressed with 9 mm flat shaped punches on a 10-station mini rotary tableting machine(Shakti Pharmatech Pvt.Ltd,Ahmedabad) at 750mg weight. Nineteen different formulas having different concentrations of hydroxy propyl methylcellulose, ethyl cellulose, eudragit RLPO and eudragit RSPO were developed to study the effect of polymer composition and concentration on drug release.

Evaluation of tablets:

Prepared tablets were evaluated for thickness, weight variation, drug content, hardness and friability according to official methods .

In-vitro drug relase studies:

In-vitro dissolution studies of acyclovir tablets were carried out in USP XXIII tablet dissolution test apparatus-II(Electrolab) employing a paddle stirrer rotating at 50 rpm. The dissolution medium consisted of 750 ml of 0.1 N Hcl (pH 1.2) for 2hours and then the pH was changed to 6.8 by adding 250 ml of 0.2 M tri sodium phosphate for the rest of the dissolution duration. The temperature of the dissolution medium was maintained at $37 \pm 0.5^{\circ}\text{C}$ throughout the experiment . 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45 μ membrane filter and drug content in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 255 nm, and cumulative percent drug release was calculated. The study was performed in triplicate. The results of dissolution studies were shown in Figure 1 and 2.

Data analysis:

To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in zero order, first order, Higuchi matrix and Korsmeyer- Peppas models. The best-fit model was selected by comparing the R² values obtained⁸.

Scanning electron microscopy (SEM)

The optimized formulation F2 was observed under scanning electron microscope (JEOL-JSM-840A, Japan) for studying surface morphology.

RESULTS AND DISCUSSION

The FT-IR Spectrum of pure Acyclovir and its physical mixture with polymers and different excipients are shown in Figure 3A to 3F . Pure acyclovir showed peaks at 3522.02cm^{-1} (O-H stretching), 1608.63cm^{-1} (O-H deformation), 3471.87cm^{-1} (1^0 N-H stretching) , 2927.94cm^{-1} (aliphatic C-H stretching anti symmetric), 2854.65cm^{-1} (aliphatic C-H stretching symmetric), 1485.19cm^{-1} (aliphatic C-H deformation), 1712.79cm^{-1} (C=O stretching) and 1105.21cm^{-1} (C-O stretching). Infrared absorption spectrum of formulation F2 shows peaks at 3520.09cm^{-1} (O-H stretching), 1610.56cm^{-1} (O-H deformation), 3469.94cm^{-1} (1^0 N-H stretching) , 2918.30cm^{-1} (aliphatic C-H stretching anti symmetric), 2850.79cm^{-1} (aliphatic C-H stretching symmetric), 1483.26cm^{-1} (aliphatic C-H deformation), 1716.65cm^{-1} (C=O stretching) and 1105.21cm^{-1} (C-O stretching). As the sharp characteristic peaks of acyclovir did not change in physical mixture with polymer and different excipients , indicating no possible interaction.

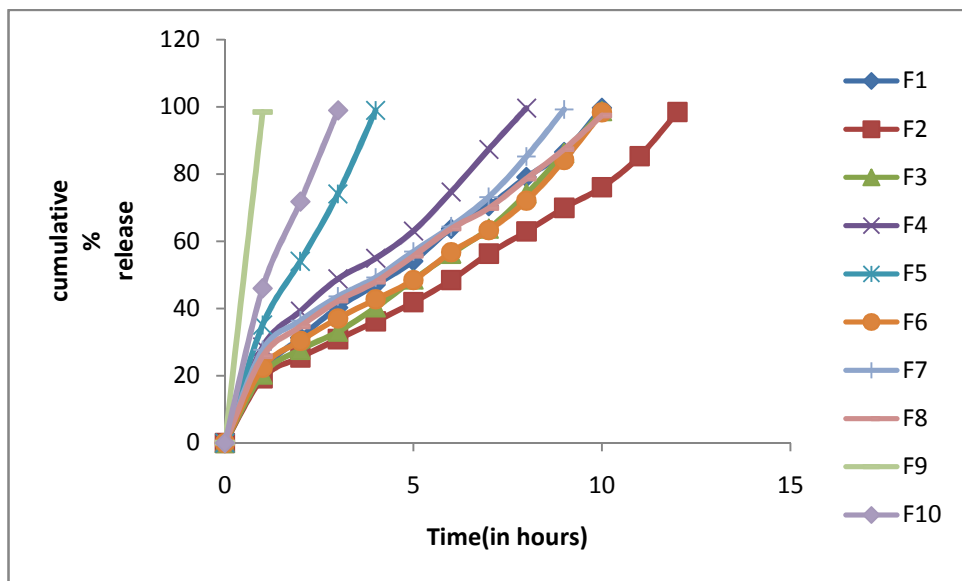


FIGURE 1. *In vitro* dissolution profile of F1to F10 formulations

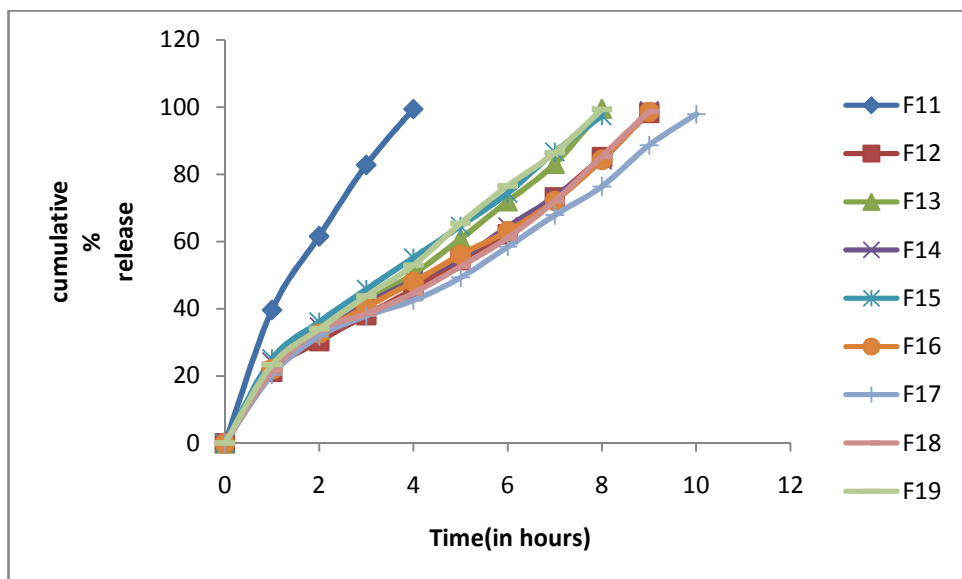


FIGURE 2. *In vitro* dissolution profile of F11to F19 formulations

Table 1: Tablet composition of different formulations of acyclovir controlled release matrix tablets (mg/tablet)

INGREDIENDS	FORMULATION CODE																		
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19
Acyclovir	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
HPMC K 100	525	450	375	262.5	--	450	375	262.5	--	--	--	375	300	375	300	375	300	375	300
Ethyl cellulose(22CPS)	--	75	150	262.5	--	--	--	--	--	150	75	75	75	75	75	75	75	75	75
Eudragit RSPO	--	--	--	--	525	75	150	262.5	--	187.5	225	--	--	--	--	--	--	--	--
Eudragit RLPO	--	--	--	--	--	--	--	--	525	187.5	225	--	--	--	--	--	--	--	--
Microcrystalline cellulose	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	77.5	152.5	--	--	--	--	--	--
Lactose	--	--	--	--	--	--	--	--	--	--	--	--	--	77.5	152.5	--	--	--	--
Di basic calcium phosphate	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	77.5	152.5	--	--
Starch 1500	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	77.5	152.5
Magnesium stearate	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5

The thermogram obtained by these studies shows DSC curves of pure acyclovir, its physical mixture of polymers and different co- excipients . A sharp endothermic peak at 256.70 was obtained for pure acyclovir corresponding to its melting point . The endothermic peak of formulation F2 showed at 246.49 due to various concentration of physical mixture . Thus these minor changes in the melting endotherm in the drug would be due to the mixing of the drug and excipients which lower the purity of each component in the mixture. As melting point of acyclovir and the formulation F2 are nearer did not show major change , indicating no possible interaction shown in Figure 4a to 4d . The prepared tablets were evaluated for weight variation, hardness , friability , thickness and drug content and were found to be in the range of 748.85 ± 0.45 to 754.95 ± 0.32 , 6.00 ± 0.46 to 8.00 ± 0.03 , 0.26 to 0.75, 6.10 ± 0.10 to 6.52 ± 0.10 and 98.22 ± 0.20 to 101.30 ± 0.36 . The formulated matrix tablets met the pharmacopoeial requirement of uniformity of weight. All tablets conformed to the requirement of drug content, hardness , friability and thickness. Marketed formulation (Herperax 200mg, Micro labs limited) released all the drug content in 10 minutes. The amount of acyclovir released from formulation F-1 to F-11 and F12 to F19 at first hour ranged between 19.23% to 45.97% and 20.38 % to 25.10 % (Figure 1 and 2).

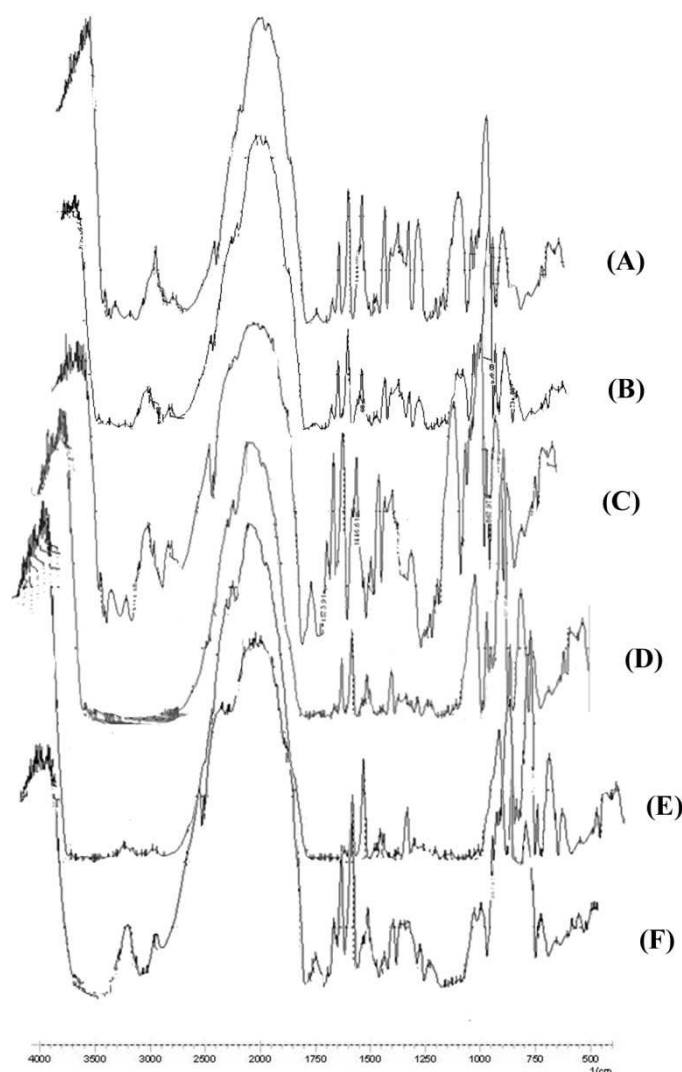


FIGURE 3. The FT-IR spectra of pure acyclovir(A), acyclovir with HPMC K100(B), acyclovir with ethyl cellulose (C), acyclovir with eudragit RSPO (D), acyclovir with eudragit RLPO (E), and Acyclovir+hydroxy propyl methyl cellulose K100+ ethyl cellulose + microcrystalline cellulose +magnesium stearate + talc (formulation)F2(F)

Polymer HPMC K100 has been well known to retard the drug release by swelling in aqueous media. A polymer's ability to retard the drug release rate is related to its viscosity. Processing factors including particle size, hardness, porosity and compressibility index etc. also can affect the release rate of drug from tablets⁹. The hydration rate of HPMC depends on the nature of the substituent's like hydroxypropyl group content. Hence, HPMC K100 was used because it forms a strong viscous gel in contact with aqueous media which may be useful in controlled delivery of drug¹⁰. During first hour tablets containing HPMC K 100 alone F1(70% HPMC K 100) showed initial burst

release of 21.19 %. At the end of 10 hours 99.64 % of drug was released from the formulation F1, did not provide a controlled release. Hence, it was necessary to control the initial burst release, ethyl cellulose was included in the matrix along with HPMC K 100. Formulation F3 (50% HPMC K 100 and 20% EC) and F4 (35% of HPMC K 100 and 35% EC), were able to sustain the drug release for 10 and 8 hours respectively.

Among the different formulation, matrix tablets containing blend of HPMC K100 and EC in the ratio 60%:10%, presented large extent of slower release, in first hour 19.23 % of drug was released, later it followed release of drug by sustained manner for the period of 12 hours with 98.39 %. Good release retardant effect obtained from ethyl cellulose because of its hydrophobic nature, less permeation of dissolution medium there by decrease of drug diffusion.

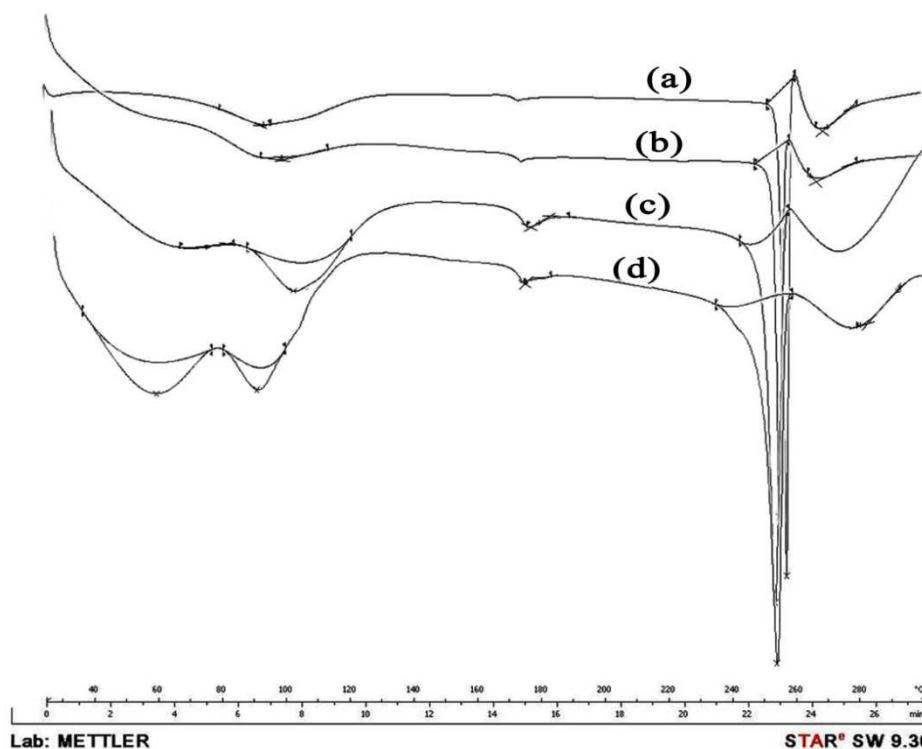


FIGURE 4. DSC thermogram of pure acyclovir (a), acyclovir with HPMC K100 (b), acyclovir with ethyl cellulose (c), and Acyclovir+hydroxy propyl methyl cellulose K100+ ethyl cellulose + microcrystalline cellulose +magnesium stearate + talc (formulation)F2 (d)

Formulation F5(70% eudragit RSPO) could able to control release up to 4 hours. It is due to nature of very low water solubility, low content of quaternary ammonium compound and reduced permeability of eudragit RSPO.

Formulation F6(60% of HPMC K 100 and 10% of eudragit RSPO),F7 (50% of HPMC K 100 and 20% of eudragit RSPO) and F8(35% of HPMC K 100 and 35% of eudragit RSPO) were able to sustain release for 10,9and 10 hours respectively.

Formulation F9(70% eudragit RLPO) showed poor release of controlling capacity of acyclovir, released 98.42% of drug at the end of 1 hour. Even by incorporating 70% eudragit RLPO of in the formulation the release rate could not be sustained for more than 1 hour. Tablets were disintegrated in 1hour. More permeability, good swelling, the additional number of quaternary ammonium groups, and the concentration of eudragit RLPO was not sufficient enough to control the release for long period of time, this were the reasons for the above. Formulations that contained triple mixture of ethylcellulose, eudragit RSPO and eudragit RLPO (Formulation F10 and F11) were ineffective in controlling release of acyclovir. Concentration of polymer present in tablet containing triple mixture was not sufficient enough to control the release beyond 4 hours. Formulations F12 to F19 were prepared to find the effect of fillers. Concentration of 10% and 20% of various fillers were used, HPMC K 100 and ethyl cellulose were used at 50%, 40% and 10% concentration in formulations F12 to F19.

Formulations F12, F14,F16, F18 and F13, F15,F19 were able to sustain release for 9 and 8hours respectively. Compared to other formulation containing fillers, the formulation F17 had more controlled release it released up to 10 hours. Solubility, hydration and relaxation character of lactose gave more dissolution and diffusion of drugs

than other fillers. A reduced amount of drug was released due to insoluble, less swelling and erosion nature of dibasic calcium phosphate. Major difference in drug release did not obtained from the fillers of microcrystalline cellulose and starch1500. The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F1 to F19, could be best expressed by Zero order equation as the plots showed highest linearity (R^2 : 0.978 to 0.999), when compared with First order release kinetics (R^2 : 0.619 to 0.870). All the formulations were shown good fit in the following order of Zero order > Korsmeyer Peppas (R^2 : 0.956 to 0.999) > Higuchi (R^2 : 0.928 to 0.997) > First order. The n values obtained from Korsmeyer Peppas plots ranges from (0.5589 to 0.7353) indicate that mechanism of release of formulations F1 to F19 was Anomalous (non-Fickian) diffusion mechanism. Therefore drug release from the matrix tablets is by both diffusion and erosion.

The SEM photographs of the formulation exposed that the formation of pores throughout the matrix with time and gelling structure on tablet surface, which is clearly indicated the involvement of both diffusion and erosion mechanisms to be responsible for sustaining the release of acyclovir from formulated matrix tablets F2 shown in Figure 5.

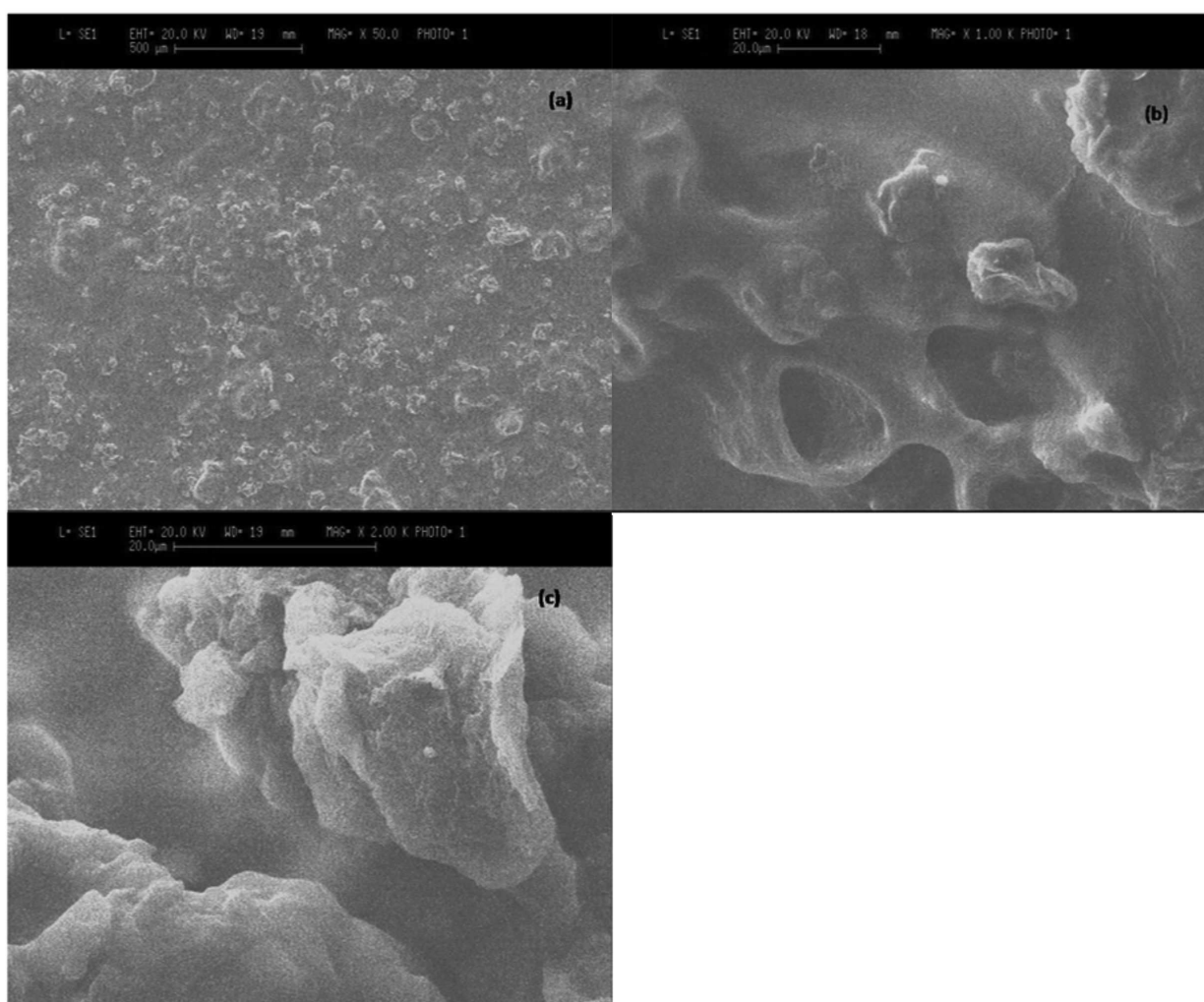


FIGURE 5. SEM photographs of matrix tablets after 2,6 and 12 hours of dissolution (a, b and c)

CONCLUSION

It was concluded that both HPMC K100 and ethyl cellulose can be used as an effective controlled release polymers to retard the release of acyclovir. Addition of HPMC K100 was found to be vital to control drug release. Slow, controlled and complete release of acyclovir for a period of 12 hours was obtained from matrix tablet formulated with blend of HPMC K100 and EC in of 60%:10%. The mechanism of drug release from formulation F2 was

diffusion coupled with erosion. Suitable combination and concentrations of polymers provided reasonably good controlled drug release.

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