EFFECT OF HYDROPHILIC POLYMERS ON CONTROLLED RELEASE MATRIX TABLETS OF ACYCLOVIR

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ABSTRACT

Acyclovir was formulated as oral controlled release matrix tablets using natural and synthetic 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 pharmacopoeal standards. The tablets prepared with various combination of hydroxy propyl methylcellulose (HPMC K100), locust bean gum (LBG) and karaya gum (KG) failed to produce the desired controlled release. Dissolution studies indicated that formulation F5 was most successful of the study. The formulation F5 exhibited anomalous (non-Fickian) diffusion mechanism. Based on the results of *in-vitro* studies it was concluded that the hydrophilic polymers can be used as an effective matrix former to provide controlled release of acyclovir. SEM images of tablet after dissolution showed pore formation. FT-IR and DSC study did not show any possibility of interaction between acyclovir and excipients.

Keywords: Acyclovir, Hydroxy propyl methylcellulose (HPMC K100), Locust bean gum (LBG), Karaya gum (KG).

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 its flexibility, cost effectiveness and broad regulatory acceptance. Use of hydrophilic polymers in matrix for controlled release of an active agent is a known strategy. For controlled release solid dosage form comprising a drug dispersed uniformly in hydrophilic polymers, release of drug is controlled primarily by diffusion of the drug, by surface erosion of the hydrophilic polymers in the surrounding medium, or by combination of the two processes. Hydroxy propyl methylcellulose is the dominant hydrophilic vehicle for the preparation of oral controlled drug delivery systems. Numerous studies have been reported in the literature [1, 2].

Natural gums are biodegradable and nontoxic, which hydrate and swell well on contact with aqueous media, and these have been used for the preparation of dosage form[3]. Karaya gum(KG),dry exudates of plant species *Sterculia* has high swelling property and is an important hydrogel in formulations for constant release of drug *invitro*[4]. Locust bean gum (LBG) is a plant seed galactomannan, composed of a 1-4 linked ß -D- mannan backbone with 1-6-linked α -D- galactose side groups. It is a nonionic molecule consisting of 2000 residues[5]. In LB the ratio of mannose to galactose is 4:1. It is not affected by the ionic strength or pH but will degrade at extreme (above pH 10) pH at higher temperature. LBG structure contains long stretches of bare mannose backbone (up to 80 D- mannose units long) which is responsible for synergistic interaction with other polymers and greater functionality[6, 7]. Acyclovir is a potent antiviral drug useful in the treatment of *Herpes simplex*, *Herpes zoster*, Chicken pox and HIV infection. Acyclovir has

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a short biological half life of 2.5h and also dosing frequency of 200mg/400mg 5 times a day depending upon the type of infection. An alternative dose of 800mg leads to plasma fluctuations. Controlled release formulation is needed 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 levels[8].

The objective of the present work is to develop controlled release matrix tablets of acyclovir by using different hydrophilic matrix polymers alone or in combination and study the polymer concentration effect on release pattern.

MATERIALS AND METHODS

Acyclovir was obtained as gift sample from Arochem Industries (Mumbai). Karaya gum, HPMC K 100 and Locust bean gum were purchased from Research Lab Fine Chem Industries (Mumbai),Micro crystalline cellulose was procured from Loba Chem Pvt. Ltd, (Mumbai). Magnesium stearate and talc was obtained from S.D. Fine Chem Ltd (Mumbai). 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 its respective physical mixtures were taken to assure the compatibility between pure acyclovir and them. 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 I. 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) at 750mg weight. Ten different formulae having different concentrations of hydroxy propyl methylcellulose, locust bean gum and Karaya gum were developed to study the effect of polymer 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 2 hours 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± 0.5^0 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 0.45µ 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 Fig. 1.

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 R^2 values obtained are presented in Table III[9].

Scanning Electron Microscopy (SEM)

The optimized formulation F5 was observed under scanning electron microscope (JEOL-JSM-840A, Japan) for studying surface morphology.

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

INGREDIENTS	FORMULATION CODE									
	FI	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Acyclovir	200	200	200	200	200	200	200	200	200	200
HPMC K 100	-	150	75	262.5	375	450	-	375	225	75
Locust Bean gum	525	375	450	262.5	150	75	-	75	150	225
Karaya gum	-	-	-	-	-	-	525	75	150	225
Microcrystalline cellulose	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	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

Table II : Tablet properties of the different formulations of acyclovir controlled release matrix tablets

Parameter	FI	F2	F3	F4	F5	F6	F7	F8	F9	F10
Thickness (mm)	6.29± 0.04	6.23± 0.08	6.26± 0.05	6.25± 0.03	6.28± 0.10	6.25± 0.01	6.21± 0.02	6.25± 0.04	6.24± 0.06	6.22± 0.04
Hardness (kg/cm^2)	5.0± 0.28	5.8± 0.52	5.2± 0.03	5.9± 0.13	6.5± 0.18	7.2± 0.33	4.3± 0.19	7.0± 0.03	6.3± 0.00	5.6± 0.10
Friability (%)	0.92	0.81	0.89	0.74	0.63	0.55	0.94	0.76	0.87	0.94
Drug content (%)	99.38± 0.02	99.94± 0.45	99.83± 0.39	99.86± 0.30	99.64± 0.23	98.74± 0.46	99.86± 0.08	99.92± 0.41	99.48± 0.19	99.52± 0.28

All the values are expressed as mean ±SD, n=6

Table III : Kinetics of drug release from acyclovir controlled release matrix tablets

Formulation code	Zero order regression coefficient (R^2)	First order regression coefficient (R^2)	Higuchi equation regression coefficient (R^2)	Korsmeyer et al's plots	
				Regression coefficient (R^2)	Slope(n)
F1	0.997	0.693	0.981	0.987	0.5393
F2	0.996	0.667	0.984	0.996	0.7060
F3	0.997	0.707	0.970	0.966	0.5443
F4	0.990	0.695	0.978	0.988	0.5369
F5	0.999	0.756	0.982	0.988	0.6085
F6	0.995	0.747	0.982	0.993	0.6158
F8	0.999	0.719	0.984	0.992	0.6789
F9	0.997	0.769	0.978	0.971	0.4076
F10	0.856	0.978	0.905	0.913	1.3419

RESULTS AND DISCUSSION

The FT-IR spectrum of pure acyclovir and its physical mixture with polymers and different excipients are shown in Fig. 2A to 2F. Pure acyclovir showed peaks at 3522.02cm^{-1}(O-H stretching),1608.63cm^{-1}(O-H deformation),3471.87 cm^{-1} (1^0 N-H stretching) , 2927.94 cm^{-1} (aliphatic C-H stretching anti symmetric), 2854.65 cm^{-1} (aliphatic C-H stretching symmetric), 1485.19 cm^{-1} (aliphatic C-H deformation), 1712.79 cm^{-1} (C=O stretching) and 1105.21 cm^{-1} (C-O stretching). Infrared absorption spectrum of formulation F5 shows peaks at 3520.09cm^{-1}(O-H stretching),1610.36cm^{-1}(O-H deformation),3471.87 cm^{-1}(1^0 N-H stretching) , 2918.30 cm^{-1} (aliphatic C-H stretching anti symmetric), 2850.79 cm^{-1} (aliphatic C-H stretching symmetric), 1485.19 cm^{-1} (aliphatic C-H deformation), 1714.72 cm^{-1} (C=O stretching) and 1105.21 cm^{-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.

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^{0}C was obtained for pure acyclovir corresponding to its melting point. The endothermic peak of formulation F5 showed at 251.44^{0}C due to various concentrations of the physical mixture. Thus these minor changes in the melting endotherm in the drug would be due to the

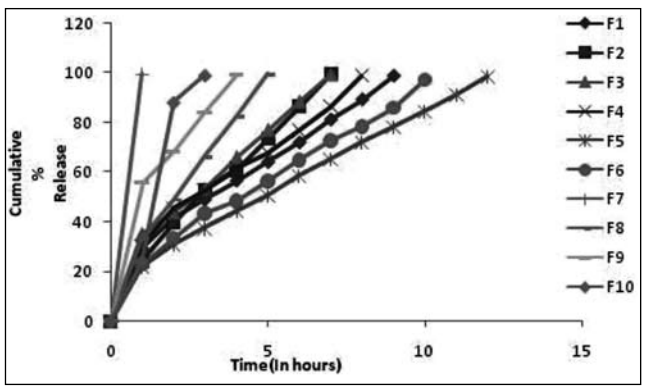

Fig. 1: *In vitro* dissolution profile of F1 to F10 formulations

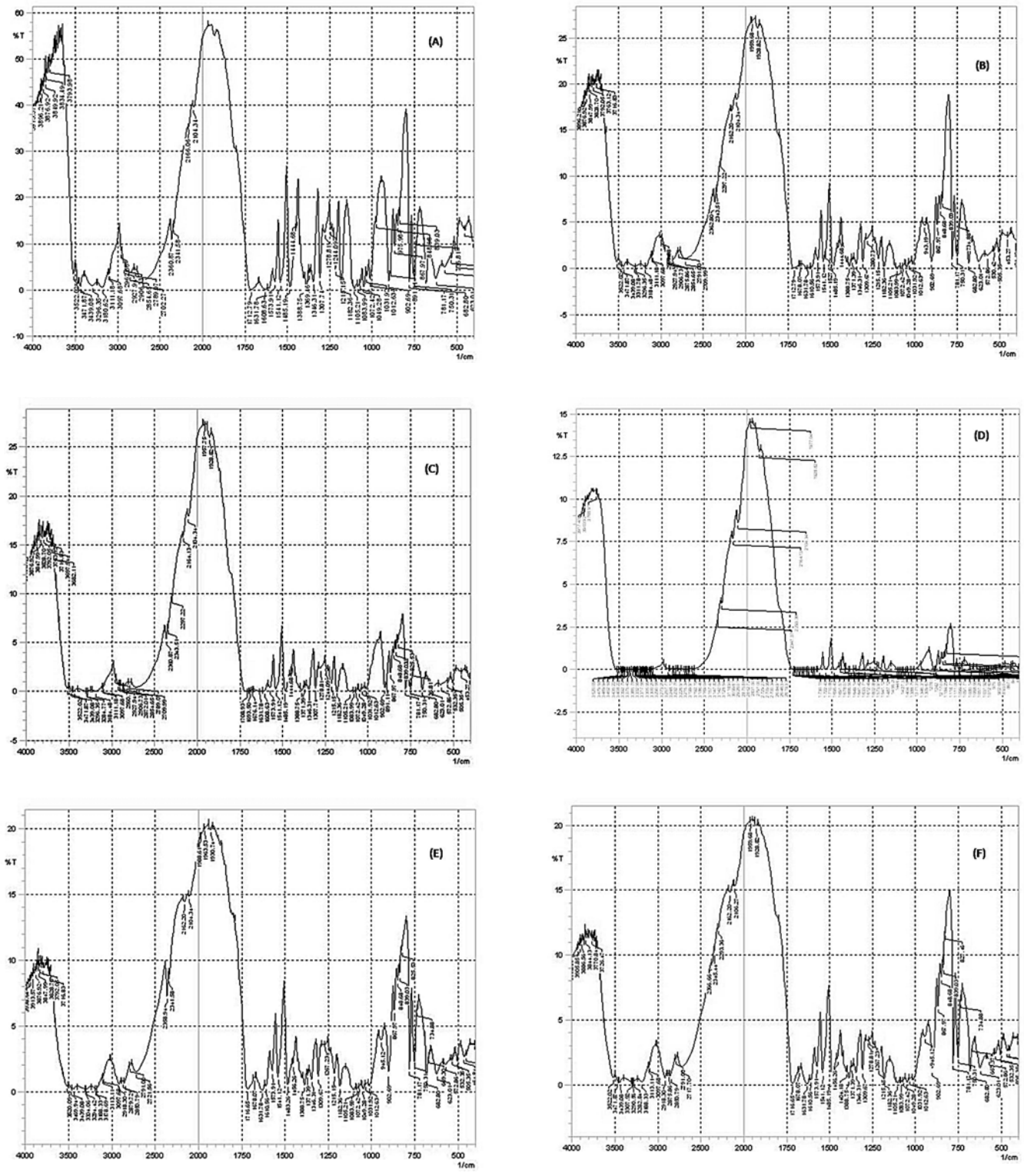

Fig. 2:The FT-IR spectra of pure acyclovir(A), acyclovir with HPMC K100(B), acyclovir with locust bean gum(C) , acyclovir with karaya gum (D) , acyclovir+hyrdoxy propyl methyl cellulose K100+ locust bean gum+ microcrystalline cellulose +magnessium stearate + talc (formulation)F5(E) , and Acyclovir+hyrdoxy propyl methyl cellulose K100+ locust bean gum+ Karaya gum +microcrystalline cellulose +magnessium stearate + talc (formulation)F8(F)

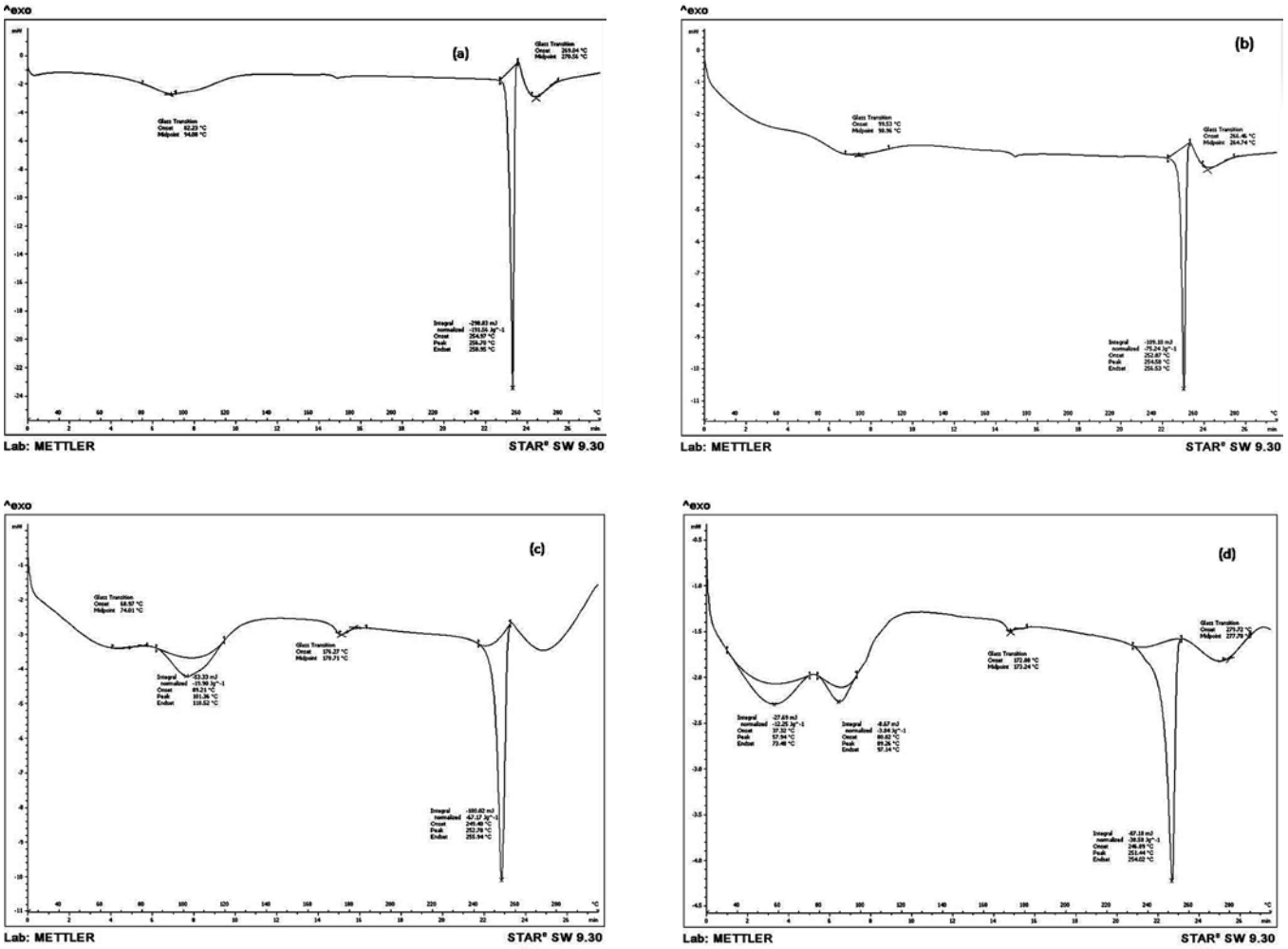

Fig. 3: DSC thermogram of pure acyclovir (a), acyclovir with HPMC K100 (b), acyclovir with locust bean gum (c), acyclovir+hydroxy propyl methyl cellulose K100+ locust bean gum+ microcrystalline cellulose +magnessium stearate + talc (d), (formulation)F5

mixing of the drug and excipients which lower the purity of each component in the mixture. As melting point of acyclovir and the formulation F5 are nearer and did not show major change, indicating no apparent possible interaction (Fig. 3a to 3d).

The formulated matrix tablets met the pharmacopoieal requirement of uniformity of weight. All tablets conformed to the requirement of assay, hardness, friability and thickness. Results are provided in Table II.

Marketed formulation (Herperax 200mg, Micro labs limited) released 100% of drug in 10 minutes. The amount of acyclovir released from formulation F-1 to F-10 at first hour ranged between 22.17 to 55.92 (Fig. 1). Formulation F2 (30% HPMC K 100 and 50% LBG),F3(10% HPMC K 100 and 60% LBG), F4(60% of HPMC K 100 and 30% LBG), were able to sustain the drug release for 7,8 and 10 hours respectively. During first hour tablets containing locust bean gum alone F1(70%LBG) showed initial burst release of 29.34 %. At the end of 9 hours 98.76 % of drug was released from the formulation F1 but did not provide a controlled release. Hence , it was necessary to control the initial burst release, HPMC K100 was included in the matrix along with locust bean gum.

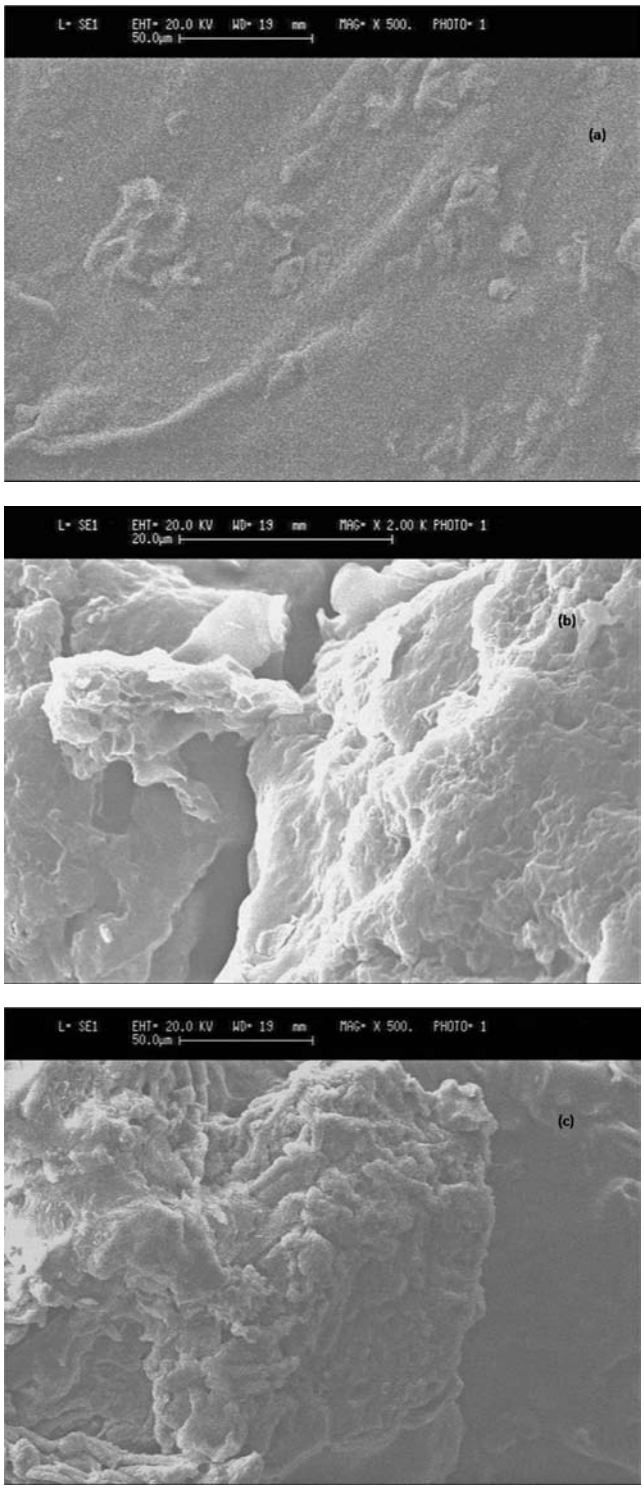

Fig. 4: SEM photographs of matrix tablets after 2,6 and 12 hours of dissolution (a, b and c)

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 also can affect the release rate of drug from tablets[10]. The hydration rate of HPMC depends on the nature of the substituents 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 drug [11].

Among the different formulations, matrix tablets containing blend of HPMC K100 and LBG in the ratio 50%:20%,could sustain the release up to 12 hours. The release from formulation F5 was found to be slower and more controlled when compared to other formulations. The high viscosity of the gel formed resulted in longer diffusional path length, resistance to diffusion and erosion of the drug is due to the gel viscosity. This synergistic effect is due to combination of HPMC K100 and LBG; similar kind of result was observed with LBG and KG matrices[7,12].

Formulation F7(70% KG) showed poor release of controlling capacity of acyclovir, releasing 99.64% of drug at the end of 1 hour . Even by incorporating 70% of karaya gum in the formulation the release rate could not be sustained for more than 1 hour . Tablets were disintegrated just within 1 hour. Formulation that contained triple mixture of karaya gum, locust bean gum and HPMC K100 (Formulation F8, F9 and F10) were ineffective in controlling release of acyclovir. Concentration of polymer present in tablet containing triple mixture was not sufficient enough to produce thick gel structure. Formulation F8 (50% of HPMC K 100, 10% of LBG and 20% of KG), F9 (30% of HPMC K 100, 20% of LBG and 20% of KG) and F10 (10% of HPMC K 100, 30% of LBG and 30%) were able to sustain release for 5,4 and 3 hours respectively.

The release data was fitted to various mathematical models to evaluate the kinetics

and mechanism of drug release. The kinetic data of formulations F1,F2,F3,F4,F5,F6,F8 and F9 could be best expressed by zero order equation as the plots showed highest linearity (R^2: 0.990 to 0.999), whereas formulation F10 followed first order release kinetics (R^2: 0.978). The n values obtained from Korsmeyer Peppas plots ranges from (0.4076 to1.3419) indicating that mechanism of release of formulations F1 to F6 and F8 was anomalous (non-Fickian) diffusion, while formulations F9 and F10 showed Quasi-Fickian diffusion and Non-Fickian super case II mechanism. Therefore drug release from the matrix tablets is by both diffusion and erosion.

The SEM photographs of the formulation revealed that the formation of pores throughout the matrix with time and gelling structure on tablet surface, which clearly indicated the involvement of both diffusion and erosion mechanisms to be responsible for sustaining the release of acyclovir from formulated matrix tablets F5 shown in Fig. 4.

CONCLUSION

It was concluded that both locust bean gum and HPMC K100 can be used as effective controlled release polymers to retard the release of acyclovir. Addition of HPMC K100 was found to be essential to control drug release. Slow, controlled and complete release of acyclovir for a period of 12 hours was obtained from matrix tablets formulated with blends of HPMC K100 and LBG in of 50%:20%. The mechanism of drug release from formulation F5 was diffusion coupled with erosion. Suitable combination and concentrations of polymers provided fairly good controlled drug release.

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