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Floating Microspheres of Ethyl Cellulose and Pluronic F127 for Controlled Release of Acyclovir

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ABSTRACT

The present work reports on the preparation of ethyl cellulose (EC)-pluronic F127 (PF127)-based tableted floating microspheres by the oil-in-water emulsion solvent evaporation method for the controlled release of acyclovir (ACV). Microspheres of this study were characterized by Fourier transform infrared (FTIR) spectroscopy to investigate the chemical interactions of ACV with the polymer, floating behavior, scanning electron microscopy (SEM) for morphology of the microspheres, differential scanning calorimetry (DSC) for investigating their thermal properties and X-ray diffraction (XRD) as well as. *In vitro* release experiments of microspheres were performed in acidic pH 1.2 media to understand the release profiles of ACV. The selected sets of microspheres were compressed into tablets using the compressible excipients and their *in vitro* release performances were evaluated in pH 1.2 media.

Keywords: Floating microspheres, tablets, ethyl cellulose, pluronic F127, Acyclovir.

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INTRODUCTION

Oral controlled release (CR) dosage formulations generally possess the transit time of 1–3 h in the stomach, 3–5 h in the intestine and 4–11 h in the colon[1,2]. However, some drugs require more retention time in the stomach for better results. Gastro-retentive drug delivery systems are superior in delivering drugs having narrow absorption window and low solubility in the intestinal pH (alkaline) as well as colonic degradation. This type of approach helps to prolong the gastric residence time, thereby targeting the site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Also, such dosages remain in the gastric region for long periods of time and thus significantly prolonging the gastric retention time of the drugs. Over the past few decades, several gastroretentive drug delivery systems have been developed, including those of swelling devices[3-5], floating systems[6-8], bioadhesive systems[9], low density systems[10], high density systems[11], expandable systems[12], superporous, biodegradable hydrogels[13,14], magnetic systems[15] and gas formation devices[16,17] mostly in the form of floating microspheres, tablets, pellets, capsules, etc. Among these, the multiparticulate systems are more effective than the single unit dosage forms[18,19].

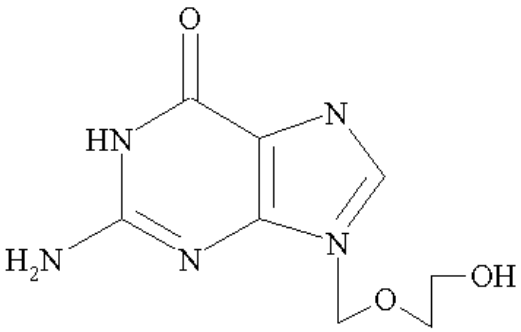

Figure 1 : Chemical structure of ACV

Pluronics, also known as poloxamers, are triblock copolymers of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) (PEO-*b*-PPO-*b*-PEO) having many pharmaceutical applications[20-22]. These are recognized as the pharmaceutical multi-purpose excipients that are capable of increasing aqueous solubility and stability of the drugs[23,24]. Pluronic F127 (PF 127) is an ABA-type triblock copolymer consisting of polyoxyethylene (A) and polyoxypropylene (B) units. The PF127 has a good solubilizing capacity with a low toxicity and is therefore, considered as a good medium for drug delivery[25]. Acyclovir (ACV), 9–[(2 hydroxyethoxy) methyl] -9H- guanine 2-amino-1, 9-dihydro-9-[(2-hydroxyethoxy) methyl]-6H-purin-6-one, is an FDA approved drug for the treatment of herpes simplex encephalitis, herpes genitalis, herpes labialis, herpes zoster, varicella (chickenpox), varicella-zoster virus and viral conjunctivitis (see its structure in figure 1)

It has a short half life of 2.5-3.3 h. with a maximum absorption in the stomach and upper part of small intestine[26]. Due to low gastric retention time, bioavailability of the drug is low because large portion of the drug misses the absorption window. Therefore, it was felt worthwhile to develop a gastric floating drug delivery system of ACV to improve the efficacy of the dosage form. Recently, some researchers[27,28] have demonstrated that tableting of microspheres is necessary to control the release of drugs. In the present work, floating microspheres of EC and PF127 were blended and used as effective CR devices for the CR of ACV. Drug-loaded formulations were characterized by Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), X-ray diffraction (XRD) and scanning electron microscopy (SEM). Drug release characteristics have been investigated in pH 1.2 media to study the variations of drug/polymer concentrations. Representative formulations were selected for compression into tablets using the excipients such as EC, poly(vinyl pyrrolidone) (PVP) and magnesium stearate (MgSt). Tableted microspheres were analyzed for buoyancy and *in vitro* release of ACV in pH 1.2 buffer media.

MATERIALS AND METHODS

Materials

ACV was received as a gift sample from Matrix Laboratories, Hyderabad, India. PF127 was obtained from Aldrich Chemical Co, Milwaukee, WI, USA. EC was obtained from Hi-media Chemicals Pvt. Ltd., Mumbai, India. Analytical reagent grade dichloromethane (DCM), Tween-80, poly(vinyl alcohol) (PVA) of molecular weight 125,000, PVP and MgSt were all purchased from s.d. Fine Chemicals, Mumbai, India. Water used was of high purity grade after double distillation and deionization.

Preparation of ACV-loaded Microspheres

Microspheres of EC and PF127 were prepared by emulsion-solvent evaporation method[29] by taking required amounts of EC, PF127 and ACV; all were dissolved in 5 mL of DCM. The solution was emulsified into 100 mL of 1 % PVA (as a stabilizer) solution to form o/w emulsion using a mechanical stirrer (IKA Labortechnik, Germany) at 600 rpm rotation speed at ambient temperature (25°C) for 3 h. The microspheres were separated using 0.2 μm membrane filter under suction vacuum, washed 2–3 times successively with distilled water to remove the surface-adhered PVA and filtered to collect the microspheres. The solid microspheres obtained were vacuum-dried at 40°C for 24 h and stored in a desiccator until further use. Different formulations were prepared by varying the amount of EC, PF127 and ACV loadings. Formulation codes and

experimental parameters are given in table 1.

Table 1: Formulation Parameters, % EE % Buoyancy, Empirical Parameters *n*, *k* and Correlation Coefficient (r^2) Values

Formulation code	EC (% w/w)	%F127 (% w/w)	ACV (%)	%EE	Buoyancy (%) from (eq. 1)	*n* from (eq. 2)	*k* x 10^2	r^2
F1	100	0	10	61	42	0.37	8.00	0.94
F2	90	10	10	63	56	0.28	14.70	0.92
F3	80	20	10	68	58	0.55	2.97	0.82
F4	70	30	10	78	62	0.40	8.09	0.75
F5	90	10	20	74	57	0.30	14.87	0.80
F6	90	10	30	80	44	0.43	6.19	0.84

1 wt.% PVA was used as a stabilizer for all the formulations.

Fourier Transform Infrared Spectral Analysis

FTIR spectral data were taken on a Nicolet (Model Impact 410, Milwaukee, WI, USA) instrument to find the chemical stability of drug in the microspheres. FTIR spectra of the placebo microspheres, drug-loaded microspheres and pristine drug were obtained in KBr pellets. Spectral scanning was done in the range between 4000 and 500 cm^{-1}.

Encapsulation Efficiency

Estimation of drug concentration was done as per the protocol adopted before[30]. Particles of known weight (~10 mg) were ground to get the powder using an agate-mortar, extracted with 50 mL of pH 7.4 buffer solution and sonicated for 30 min (UP 400s, Dr. Hielscher, GmBH, Germany). The solution was centrifuged (Jouan, MR23i, France) to remove polymeric debris and washed twice to extract the drug completely. The solution was centrifuged to remove the suspended polymer particles and the clear supernatant liquid was diluted with buffer solution. Drug was assayed using UV–VIS spectrophotometer (Model Anthelie, Secomam, France) at the fixed λ_{max} of 253 nm. The % encapsulation efficiency (EE) was calculated as explained before[30].

Floating Behavior of the Microspheres

Microspheres (about 100 mg) were placed in 100 mL simulated gastric fluid (SGF) (pH 1.2,) containing 0.02% w/v Tween 80 and stirred at 100 rpm. After 12 h, microparticles in buoyant and sinking layer were separated by filtration. Both the particles were dried in an oven at 40°C for 6 h and weighed. Buoyancy was determined using following equation[31]:

$$\text{Buoyancy (\%)} = \left[\frac{W_1}{W_1 + W_2}\right] \times 100 \qquad (1)$$

where W_1 and W_2 are the weights of floating and settled microspheres, respectively. All the

determinations were done in triplicate, but average data are used in data display and discussion of results.

Scanning Electron Microscopy

SEM images were taken using JEOL/EO model JSM-6390 (Sophisticated Test and Instrumentation Centre, Cochin University, Kochi, India). Particles were sputtered to form a thin gold coating of 10 nm to make them conducting. Before the actual measurements, samples were placed on a copper stub to obtain SEM images at different magnifications by applying a voltage energy of 20 KV.

Differential Scanning Calorimetry

Differential scanning calorimetry (Rheometric Scientific, Surrey, UK) was performed on drug-loaded microspheres, placebo microspheres and pristine drug. Samples were heated from 25° to 400°C at the heating rate of 10°C/min in a nitrogen atmosphere (flow rate of 20 mL/min).

X-ray Diffraction

Crystallinity of ACV after encapsulation was evaluated by XRD recorded for placebo and ACV-loaded microspheres as well as pristine ACV using x-Pert, Philips, UK. Scanning was done at the ambient temperature by varying the diffraction angle, 2θ up to 50^{o}.

Tableting of the Microspheres

ACV-loaded microspheres (F2) were tableted using the directly compressible EC as a diluent. PVP was used as a dry binder, while magnesium stearate was used as a lubricant. Each tablet contained 10 mg of ACV-loaded microspheres and the variations of compositions are given in table 2. Tablets were compressed using an IR hydraulic pellet maker (Riken Seiki Co. Ltd., Japan) by applying a pressure of 300 kgf cm^{-2} for 30 s of dwell time uniaxially. Exactly weighed quantity of powder mixture was filled into a die of 12.8 mm by applying a small pressure and then, hydraulic pressure was increased to form the tablet with hardness in range of 8-9 Kg/cm^2.

Table 2: Tablet's Composition, Floating Lag-Time, Floating Time, % EE, Empirical Parameters *n*, *k* and Correlation Coefficient (r^2) Values

Formulation code	EC (%)	$NaHCO_3$ (%)	Floating lag-time (sec)	Floating time (h)	% EE	*n* from (eq. 2)	*k* x 10^2	r^2
T1	74	20	11.5	8.4	96.	0.67	0.89	0.996
T2	69	30	7.8	14.3	95	0.70	0.90	0.971

Both formulations contain 5 wt.% PVP, 1 wt.% MgSt and 10 wt.% ACV

Drug Content in the Tablets

Each tablet was crushed into powder in an agate mortar, the powder was soaked in 50 mL of

double distilled water for 30 min and sonicated for 5 min. The solution was filtered to remove the undissolved debris. The clear supernatant solution was made up to volume, suitably diluted and estimated for ACV content at the λ_{max} value of 253nm[32] using UV–visible spectrophotometer.

Floating Behavior of Tablets

The time the tablets took to emerge on the surface of biological fluid (floating lag time) and the time the tablets constantly float on the water surface (duration of floating) were evaluated in a dissolution vessel filled with 900 mL of simulated gastric fluid of pH 1.2, previously set at 37ºC with a paddle rotation speed of 100 rpm[26]. The measurements were performed for each series of tablets (n =3).

***In Vitro* Drug Release from Microspheres and Tableted Microspheres**

In vitro drug release of the microspheres and tableted microspheres was investigated in 0.1N HCl aqueous media (pH 1.2). Experiments were performed in a tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight baskets (glass jars) at the stirring speed of 100 rpm. Each sample was placed in 500 mL of dissolution media maintained at 37°C. At regular intervals of time, sample aliquots were withdrawn and analyzed by UV spectrophotometer at the fixed λ_{max} of 253 nm for ACV. The already withdrawn sample media was replenished by adding 5 mL of fresh solvent to maintain the sink conditions. Triplicate data were collected and *in vitro* release curves were drawn through the average points, indicating standard deviations, which did not exceed > ±3 % in all the formulations.

Empirical Analysis of *In Vitro* Release Data

Cumulative *in vitro* release data were analyzed by using the empirical equation[33]:

$$M_t / M_\infty = kt^n \qquad (2)$$

Here, M_t/M_∞ represents the fractional drug release at time t, k is a kinetic parameter characterizing the drug-polymer interaction and n is an empirical parameter, characterizing the release mechanism. Dissolution profiles of all the formulations have been tested using the least-squares method at 95 % confidence limit in pH 1.2 buffer media. For values of n = 0.5, drug diffuses and releases out of the matrix following the Fickian release. If n > 0.5, anomalous or non-Fickian mode of transport exists. If n = 1, non-Fickian or more commonly called Case II transport occurs. If the values of n vary between 0.5 and 1.0, then transport is assumed to follow anomalous type[27,34]. Fickian diffusion occurs by the molecular diffusion of drug through the polymer matrix, creating a chemical potential gradient. Case II relaxational drug release is

associated due to the stresses involved in the polymers, which swells in water or biological fluids.

RESULTS AND DISCUSSION

Fourier Transform Infrared Spectral Analysis

FTIR spectra of (a) EC, (b) PF127, (c) placebo EC-PF127 microspheres, (d) ACV-loaded EC-PF127 microspheres and (e) pristine ACV are shown in figure 2. FTIR of EC shows characteristic –OH stretching and bending vibrations at 3464 and 1315 cm^{-1}, respectively. Peaks at 2924 and 2871 cm^{-1} are due to the aliphatic C-H stretching vibrations, while $–CH_3$ bending vibrations are observed at 1450 and 1378 cm^{-1}. Bands observed at 1111 and 1057 cm^{-1} suggests the presence of C-O and C-O-C stretching vibrations, respectively. In case of FTIR of PF127, characteristic –OH stretching and bending vibrations are seen, respectively at 3432 and 1344 cm^{-1}. The band at 1113 cm^{-1} is due to the presence of C-O stretching vibrations and the one at 844 cm^{-1} is due to symmetric C-O-C stretching vibrations. FTIR of the placebo EC-PF127 microspheres exhibit all the peaks that are characteristics of both EC and PF127 segments.

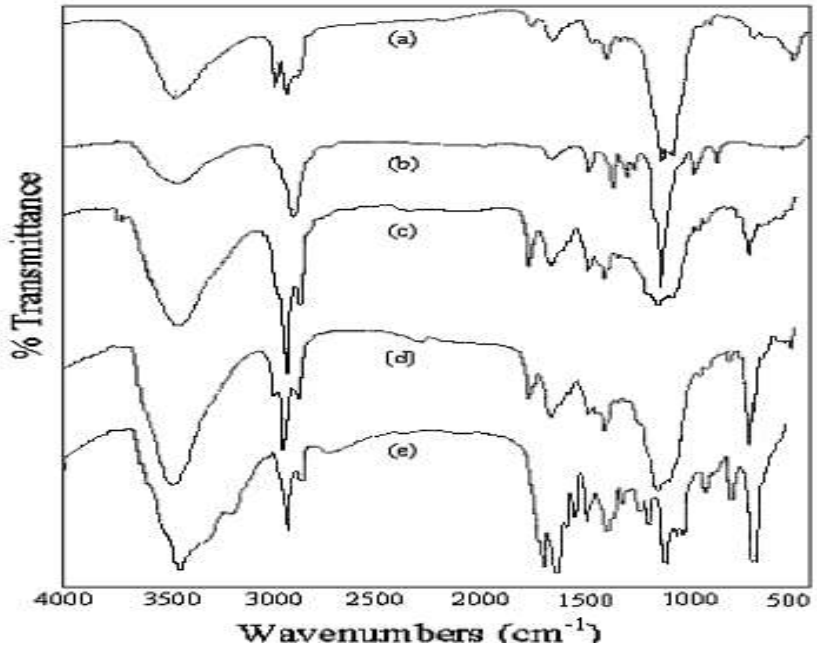

Figure 2: FITR spectra of (a) EC,(b)F127, (c) Placebo EC-F127 microspheres(d) ACV-loaded EC-F127 microspheres and (e) pristine ACV

In the case of pristine ACV, the bands at 3441 and 3312 cm^{-1}, respectively reveal the presence of both N–H and O–H stretching vibrations and the bands appearing at 2930 and 2880 cm^{-1} show the presence of aliphatic C–H stretching vibrations. A band at 1696 cm^{-1} is attributed to C=O stretching vibrations (amide-I), whereas the bands appearing at 1632 and 1388 cm^{-1} represent

amide-II and amide-III bands, respectively[32]. In case of drug-loaded microspheres, all the bands observed in ACV in addition to placebo microspheres have appeared, which confirmed the absence of chemical interactions between the drug and the polymer matrix.

Encapsulation Efficiency

The % EE of formulations varied from 61 to 80. With increasing the drug-loading of the matrix from 10 to 30 wt. %, the % EE also increased from 63 to 80, probably due to the accumulation of more of drug particles at higher loading. The % EE is higher for formulations that contained 30 wt. % of PF127 compared to 10 and 20 wt. % of PF127 (see table 1), due to the formation of a semi-solid gel of PF127 that retains more of drug particles during the preparation of microspheres. However, due to higher amount of PF127, the viscosity of polymer solution increases, thus producing bigger droplets[20].

Floating Behavior

Floating drug delivery systems are one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability to the patient. These delivery systems are desirable for drugs having an absorption window in the stomach or in the upper small intestine. Muniyandy and Boddapati[35] evaluated the EC-PEG floating microspheres loaded with ranitidine hydrochloride by the novel solvent evaporation-matrix erosion method to observe that the microspheres could float for 12 h without and 10 h with drug and were also effected by the polymeric blend ratio. Floating properties of the microspheres were studied by placing them in 0.1N HCl containing 0.02% (w/v) Tween 80 surfactant to simulate gastric conditions (figure 3). However, 0.02% Tween 80 was used to account for the wetting effect of natural surface active agents such as phospholipids in the GIT[29]. Despite the solution being stirred for >6 h, hollow microspheres still floated, indicating that microspheres are buoyant.

Floating ability of different formulations was found to be differed according to the polymeric blend ratio. For instance, formulation F1 showed a 42 % of floatability, whereas formulations containing 10 wt. % of PF127 showed a somewhat lesser floatability than those containing 20 and 30 wt. % of PF127. For instance, formulations F2 and F3 showed lesser buoyancy compared to F4, due to the fact that with increasing amount of PF127, the hydrophilicity of the matrix increased, leading to the dissolution of more of PF127 from the microspheres. Such a dissolution of PF127 might have produced a large number of pores on the surface of the microspheres as evidenced by the SEM (see figure 4). The buoyancy effect decreased from 56 to 41 % as the drug-loading in the matrix increased from 10 to 30 wt. %. This may be due to the increase in density of the microspheres at higher drug-loading (see the results in table 1). Similar findings

have also been reported earlier[29].

Figure 3: Floting photograph of drug-loaded microspheres and (b) tablet

Scanning Electron Microscopy

SEM images of the microspheres taken at 1,00X, 500X, 1,500X and 5,000X magnifications are shown in figures 4(a), (b), (c) and (d), respectively for group of placebo microspheres, drug-loaded microspheres, individual drug-loaded microsphere and surface of drug-loaded microsphere. For drug-loaded microspheres, i.e., formulation F2 (90 wt. % EC + 10 wt. % PF127 with 10 wt. % ACV) as shown in table 1, more dents are observed compared to placebo microspheres, which will be responsible for the CR of the drug. Microspheres are all spherical in shape having the smooth surfaces with the sizes of the individual microspheres being around 50-100 μm. However, polymeric debris seen around some of the microspheres is probably due to the method of particle production.

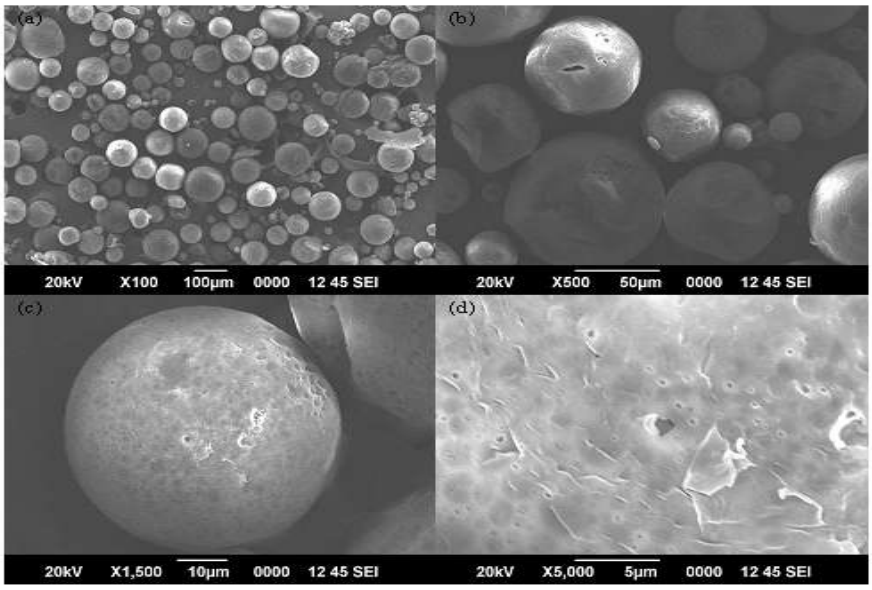

Figure 4: SEM pictures of (a) group of placebo-loaded microspheres,(b)drug-loaded microspheres,(c)individual drug loaded microspheres and (d) surface of drug-loaded microspheres

Differential Scanning Calorimetry

DSC thermograms of (a) placebo microspheres, (b) drug-loaded microspheres and (c) pristine ACV are displayed in figure 5. In case of placebo microspheres, a broad peak is observed at ~50ºC due to the endothermic transition, but the thermogram of ACV showed a sharp peak at 250ºC, indicating its melting point. In case of drug-loaded microspheres, the peak observed in placebo microspheres is noticed along with an endothermic peak around 250ºC, indicating the crystalline dispersion of drug into the polymer matrix.

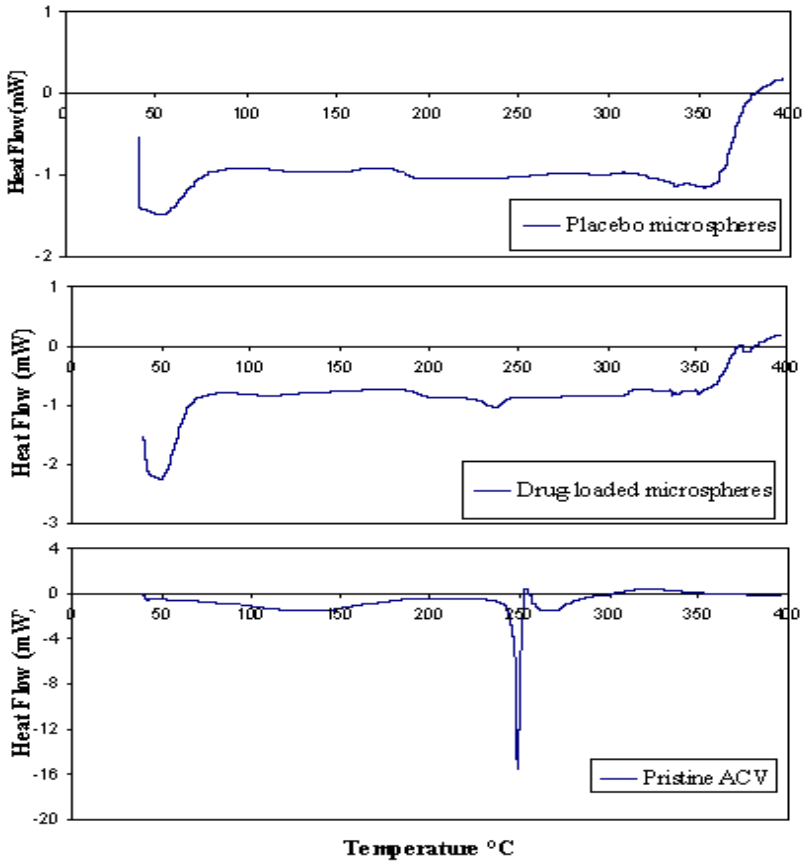

Figure 5: DSC thermograpms of (a)placebo microspheres (b) drug loaded microspheres and (c) pristine acyclovir

X-Ray Diffraction

X-ray diffractograms of (a) placebo microspheres, (b) drug-loaded microspheres and (c) pristine ACV are displayed in figure 6. These data are useful to investigate the crystallinity of ACV in the polymer matrix. For instance, the diffraction patterns of ACV have many peaks for 2θ of 6˚ to 29˚ due to its crystalline nature, but in case of placebo microspheres, no peaks are observed in this range, but in case of ACV-loaded microspheres, intense peaks are observed, indicating the crystalline nature of ACV even after encapsulation.

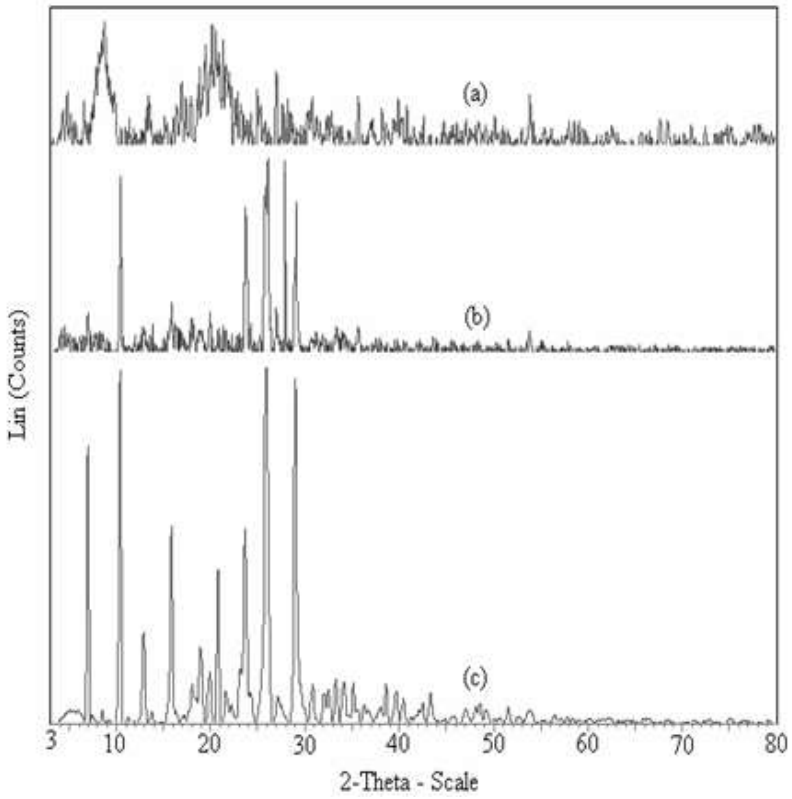

Figure 6: X-ray diffractogram of (a)placebo microspheres (b) drug loaded microspheres and (c) pristine acyclovir

Drug Content in Tablets

Drug content was analyzed on two different tablets of each formulation individually, but only the average values are presented in table 2. Notice that drug content varied between 95.87% and 96.23%.

Floating Behavior of Tablets

Recently, researchers[36,37] have developed the gas generating systems to enhance the floating behavior of matrices using different gas generating agents. Of these, sodium bicarbonate is the more frequently used gas generating agent, which induces CO_2 generation in the presence of a dissolution medium (simulated gastric fluid). The gas generated is trapped and protected within the gel formed by the hydration of the polymer, thus decreasing the density of the tablet below 1 g/mL such that the tablet becomes buoyant (figure 7). To study the effect of sodium bicarbonate concentration on floating lag-time, we have varied the concentration of sodium bicarbonate from 20 wt. % to 30 wt. %. It was found that as the concentration of sodium bicarbonate increases, the floating lag-time decreases, but the floating time increases. Floating lag-time and total duration of the floating of all the formulations are given in table 2.

Figure 7:floting photograph of drug-loaded tablet

***In Vitro* Drug Release Studies**

In order to investigate the release profiles of ACV through the matrices of this study, *in vitro* experiments were conducted in simulated gastric fluid (SGF) media (at 37°C) that contained 0.02% (w/v) of Tween 80. The release data were generated in terms of different drug loading as well as polymer compositions, i.e., by varying the amount of PF127.

The effect of drug loading on *in vitro* release profiles for formulations F2, F5 and F6 are compared in figure 8. Formulation F6 (30 wt. % of ACV) shows a higher release than F5 (20 wt. % of ACV) and similarly, F5 showed a higher release than F2 (10 wt. % of ACV). Release data of the formulations F5 and F6 have shown initial burst release of ACV, possibly due to the direct exposure of the matrix to the dissolution media with a quick release of ACV from the surface of the microspheres. This observed initial quick release of the drug is useful to achieve the therapeutic plasma concentration in a short time along with a constant release at longer time, thus facilitating the CR of ACV. With increasing drug loading, more of drug will be accumulated into the polymer matrix, giving higher drug release. Thus, release is higher for formulations that contained higher amount (30 wt. %) of drug and vice versa. In case of F2, the burst effect is minimum and the slow release occurred up to 22 h. Results of the effect of PF127 content in formulations F1, F2, F3 and F4 on their release rates are displayed in figure 9. The % cumulative release is higher for F4 (30 wt. % of PF127) than F3 (20 wt. % of PF127), F2 (10 wt. % of PF127) and F1 (0 wt. % of PF127) formulations. Formulation F3 shows a higher release rate than F2 and F1 formulations. Similarly, F2 exhibits higher release than F1. PF127 contains approximately 70% ethylene oxide, which accounts for its hydrophilicity[25]. With increasing amount of PF127, hydrophilicity of the matrix has increased, thereby enhancing the drug release

from the microspheres. Alternatively, the increased ethyl cellulose concentration might have led to increased density of the polymer matrix, resulting in an increased diffusional path length and consequent retardation of drug release[38]. Notice that for formulations F3 and F4, burst effect is more pronounced than observed for F1 and F2.

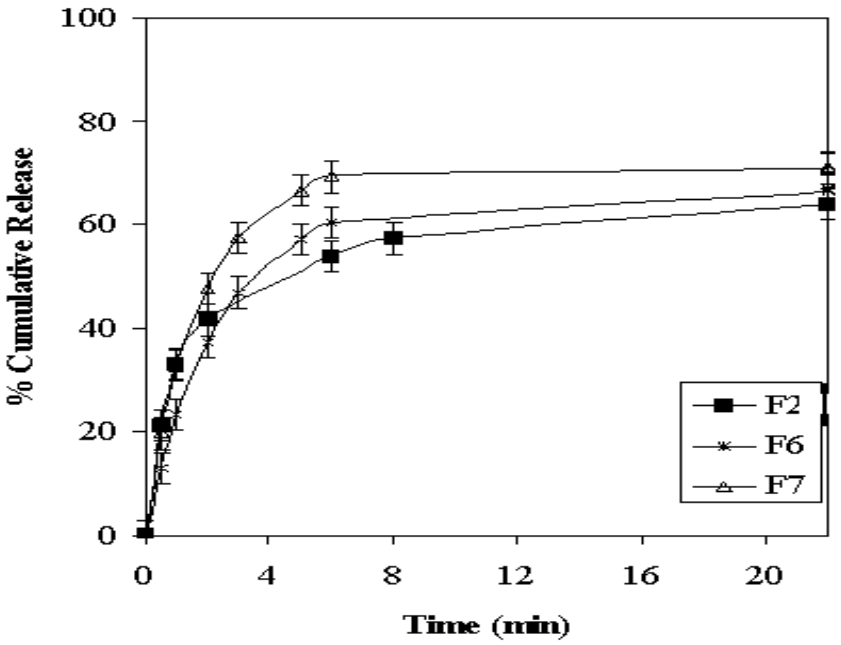

Figure 8:Effect of drug loading on in vitro release profiles for formulations F2(10 wt% ACV), F5(20 wt% ACV) and F6 (30 wt % ACV)

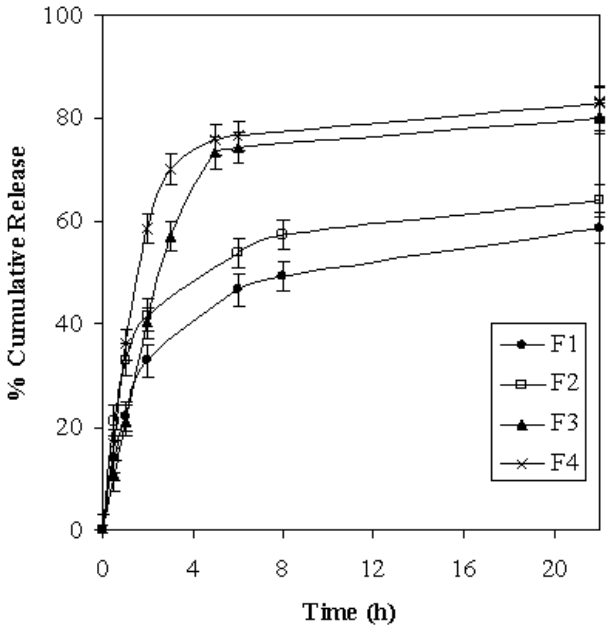

Figure 9: Effect of polymer composition on in vitro release rated of formulations F1(0wt %F127), F2 (10 wt % F127), F3 (20 wt % F127) and F4 (30 wt % F127)

The ACV tableted microspheres were prepared using the excipients as shown in table 2. Results of % drug release vs. time from the tableted microspheres are presented in figure 10. The % cumulative release of ACV from tableted microspheres is smaller than those observed for microspheres. Comparatively, high drug release rates are observed initially due to immediate dissolution of the surface-adhered ACV particles. After tableting, the initial burst release was moderately reduced due to small surface area of the tableted microspheres. Also, coating of the microspheres by hydrophobic excipients like magnesium stearate during the preparation of tablets might be responsible in reducing the burst effect. To study the effect of the amount of sodium bicarbonate on drug release, the concentration of sodium bicarbonate was varied from 20-30 wt. %. It was observed that with increasing concentration of sodium bicarbonate, the floating-lag time decreased, but the floating duration increased (table 2). Tableted formulation T1 containing 74 wt. % EC and 20 wt. % $NaHCO_3$ showed a higher % release than that of T2.

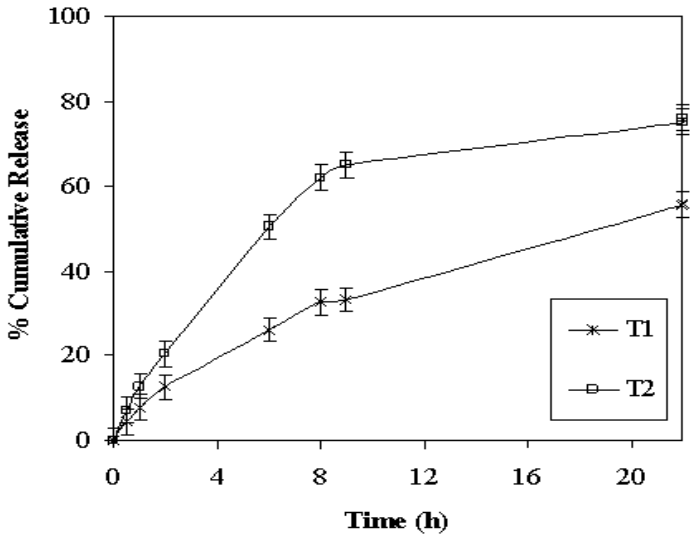

Figure 10 : Plot of % drug release vs time for tableted microspheres

Using the Korsmeyer and Peppas equation, the *n* values were obtained, which varied between 0.28 and 0.55 (table 1) for all the microspheres, whereas for the tableted formulations T1 and T2, the *n* values varied between 0.67 and 0.70 (see table 2), suggesting anomalous transport kinetics (non-Fickian trend) in both the types of formulations.

In both the microsphere as well as tableted formulations, the polymer relaxation seems to control the dissolution process. This was also apparent from the *n* values obtained, which indicated the anomalous transport trends. In general, the relaxational contribution seems to be higher for formulations with higher *n* values. The T1 and T2 formulations showed the highest contribution due to polymer relaxation effects in addition to swelling/erosion phenomenon. On the other

hand, floating microspheres showed lower *n* values, suggesting a smaller relaxational contribution during the *in vitro* release of ACV.

CONCLUSIONS

This work reports on the preparation of ACV-loaded microspheres by the solvent evaporation method using EC-PF127 blend matrices. The stable formulations were obtained without undergoing any chemical changes or degradation. Thermal studies confirmed the crystalline dispersion of the drug in the polymer matrix. The release of drug from the microspheres showed a dependence on polymer blend composition as well as the amount of drug loading. *In vitro* drug release followed the anomalous to Fickian transport trends. Tableted microspheres exhibited a good floating behavior and tableted microspheres appear to be useful in reducing the initial burst release. *In vitro* release studies indicated that the tableted microspheres of this study may be used successfully as CR devices for releasing ACV.

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