

## Optimizing the Role of Polymer Blend in the Preparation of Acyclovir Controlled-Release Tablets: An Approach for Better Patient Compliance

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### Abstract:

This study was carried out to formulate and evaluate controlled release (CR) matrix tablets of Acyclovir using combination of hydrophilic and hydrophobic polymers. Acyclovir is a guanine derivative and its half-life is short hence administered five times a day using immediate release tablets. Six formulations (F1-F6) were developed using Ethocel and Carbopol in equal combinations at drug-polymer (D:P) ratio of 10:5, 10:6, 10:7, 10:8, 10:9 and 10:10. Solubility study was performed using six different solvents. The compatibility studies were carried out using FTIR and DSC. According to USP, Quality Control and dimensional tests (hardness, friability, disintegration and thickness) were executed. *In-vitro* drug release studies of Acyclovir was carried out in dissolution apparatus using 0.1 N HCl medium at constant temperature of  $37 \pm 0.5$  °C. In order

to analyze the drug release kinetics, five different mathematical models were applied to the release data. The results showed that there was no incompatibility between drug and polymers. Physical QC tests were found within limits of USP. The release was retarded upto 24 hrs and non-fickian *in-vitro* drug release mechanism was found. A formulation developed using blend of polymers, showed excellent retention and desired release profiles thus providing absolute control for 24 hrs.

**Keywords:** Acyclovir, Carbapol, Ethocel

## 1. Introduction

The most frequently used route for administration of drugs is the oral route. The best and prevalent oral formulations available in the market are tablets and are favored by both patients and physicians equally. The most preferred formulations for chronic therapy are controlled release (CR) tablets for the reason that they offer better patient compliance [1]. The main objective of controlled release formulation is to offer appropriate carriage profiles in the range of therapeutic window [2-4].

The nature and characteristics of polymer play a significant role in release of Drug from reservoir, therefore their application can generate well branded dosage forms [1].

Among the most predominant means for oral controlled delivery of drug is the system of hydrophilic matrix and the principal of release of drug from hydrophilic matrices is based on swelling of the polymer when it interacts with the aqueous medium. The release of drug occurs then by means of diffusion, dissolution, and erosion [5-8].

The success of Acyclovir in treating *Herpes simplex* virus (HSV) has prompted the synthesis of several structural analogs, but none has shown to be as tolerable as and have shown to have such a high therapeutic index as acyclovir [9].

The most extensively used drug for genital herpes, cutaneous herpes, chicken pox, varicella zoster and herpes keratitis infections is Acyclovir. Generally acyclovir is used as 200 mg tablets orally, five times a day [8]. Acyclovir is available in conventional immediate release tablet dosage form, Intravenous infusion (Zovirax<sup>®</sup>) and 3% ocular ointment, Liposomal, niosomal and magnet depot technology have also been investigated for the acyclovir by certain researchers [10,11]. Ethyl cellulose is an important polymer excessively used as drug retarding ingredient in the formulating sustained and controlled

release pharmaceutical drug products. Ethyl cellulose alters the length and size of the diffusion path thereby controlling the release of the drug from the dosage form.

Carbomer is soft and white colored powder which can easily absorb water forming thick solutions and/ or gels. Carbomer is an inert, unchanging or stable substance. It has no any toxic effects and repel putrefaction and spoilage.

## **2. Materials and Methods**

### **2.1. Chemicals**

Acyclovir was provided as a gift sample from Glitz Pharmaceuticals, Islamabad, Pakistan. Potassium Phosphate Monobasic and Sodium Hydroxide were purchased from CBW Chemie GmbH Bitterfeld-Wolfen, Germany, Magnesium Stearate and Lactose was obtained from BDH Chemical Ltd, Pool England while Ethocel and Carbopol were taken from Dow Chemical Co. Midland USA. All the stated above chemicals were used without any further purification.

### **2.2. Instruments**

The following instruments were used during this project. Dissolution Apparatus (Curio Pak, DL 0702), UV-Visible Spectrophotometer (1800 Shimadzu, Japan), Single Punch Tablet Machine (ZT, China), Hardness Tester (Curio Pak, HT 0321), Friability Apparatus (Curio Pak, FB 0498), Disintegrating Apparatus (Curio Pak, DT 0601).

### **2.3. Construction of Standard Calibration Curve of Acyclovir**

For stock solution preparation 25 mg of Acyclovir was taken in 50 ml (0.5 mg/ml) of monobasic phosphate buffer (pH 7.4) and was placed in ultra sonifier until the drug dissolution ensured completely. Suitable dilutions were prepared from the stock solution

in descending order and then analyzed by means of UV-Spectrophotometer at  $\lambda$  max (254 nm). The corresponding absorbance values were noted and documented.

#### **2.4. Chemical Integrity**

FTIR spectra were measured for CR tablets of Acyclovir in order to investigate the effect on the functional group of Acyclovir. All samples were analyzed by a universal FTIR spectrum series at a resolution of  $4\text{ cm}^{-1}$ . For this purpose one sample of suitable quantity of pure drug and other containing pure drug along with polymers and excipients.

#### **2.5. Thermodynamic Behavior**

The thermal behavior of the prepared pure acyclovir powder and CR tablets of Acyclovir (Pure Acyclovir+polymers) was tested by Differential Scanning Calorimeter (DSC). Samples of specified quantity were placed in platinum crucible with heating range of 25–500 °C having a heating rate of  $10\text{ }^{\circ}\text{C min}^{-1}$ .

#### **2.6. Solubility Study of Acyclovir**

According to the technique described by Higuchi and Connors solubility study was performed. Six different solvents i.e. Monobasic potassium phosphate buffer having pH 7.4, 7.2 and 6.8, purified water, 0.1 N Hydrochloric acid (HCl) solution and 0.1 N Sodium hydroxide (NaOH) solution were used for solubility.

#### **2.7. Acyclovir Tablet Formulation**

Acyclovir controlled release tablets (500 mg), comprising 200 mg of Acyclovir and co-polymers Ethocel and carbopol were formulated. The tablets were prepared at several drug-to-polymer ratios (D:P ratio of 10:5, 10:6, 10:7, 10:8, 10:9, and 10:10) using the slugging method and wet granulation method. Lactose was added as a diluent and magnesium Stearate (0.5% w/w) was used as a lubricant as given in table 1.

**Table 1: Composition of 500 mg controlled-release matrix tablets comprising Acyclovir: Ethocel: Carbopol (D:P Ratio 10:5, 10:6, 10:7, 10:8, 10:9, and 10:10)**

Formulation code	Acyclovir (active)	D:P Ratio	Polymers		Filler (lactose)	Lubricant (Mg.Stearate)	Net Weight
			Carbopol	Ethocel			
<b>F1</b>	200 mg	10:5	50 mg	50 mg	197.5 mg	2.5 mg	500 mg
<b>F2</b>	200 mg	10:6	60 mg	60 mg	177.5 mg	2.5 mg	500 mg
<b>F3</b>	200 mg	10:7	70 mg	70 mg	157.5 mg	2.5 mg	500 mg
<b>F4</b>	200 mg	10:8	80 mg	80 mg	137.5 mg	2.5 mg	500 mg
<b>F5</b>	200 mg	10:9	90 mg	90 mg	117.5 mg	2.5 mg	500 mg
<b>F6</b>	200 mg	10:10	100 mg	100 mg	97.5 mg	2.5 mg	500 mg

## 2.8. Preparation of CR Tablets

Formulations of all D:P ratios were mixed in a geometrical manner with the help of pestle and mortar for obtaining uniform mixture. The lubricant (Magnesium stearate) was not added in this mixture. 10% Poly Vinyl Pyrolidone (PVP-K 30) solution was used as wetting agent. Subsequently the resultant humid mass was forcefully passed through sieve having mesh size number 8 for obtaining uniform size granules. The granules were kept for drying in tray dryer and sieving process was repeated with mesh size number 12. After drying, these granules were again passed through #12 mesh screens to avoid formation of any lumps agglomerates. Later on when dried uniform size granules were obtained, lubricant was added to the dried granules of all formulations in specified amount. Final formulations of all ratios were eventually compressed into CR tablets of Acyclovir by single punch tablet machine.

### **2.9. Determination of Tabletting Parameters**

After preparation of CR tablets of Acyclovir using wet granulation technique, they were subjected to various quality control tests for their physical characteristics investigation. Using standard operating procedure as described in USP their disintegration, thickness,, friability and hardness were determined. Digital vernier caliper was used for the thicknesses determination of all formulations. Friability, hardness and disintegration of all formulation were performed according to the standards of United State Pharmacopoeia (USP) protocol;s using hardness Apparatus, Friabililator and Disintegration Apparatus.

### **2.10. In Vitro Drug Release**

Acyclovir CR tablets of all formulations were examined using USP Method-1 (Rotating Basket Method) for *in vitro* release studies. The media used, was 0.1 N HCl which was

kept at temperature of  $37 \pm 0.5$  °C. 5 ml sample was taken with the help of syringe from each basket at definite intervals of time (1, 2, 3, 6, 8, 9, 10, 12, 15, 18, 24 hours). 5 ml solvent was added to each basket so that net volume remains constant. All the samples were filtered by membrane filter having size of  $0.45 \mu\text{m}$  before taking their absorbance so that any extra particles or can be removed from samples. Absorbance of all sample were obtained with the help of UV-Visible Spectrophotometer at 254 nm and their percentage releases of each formulation were determined.

### 2.11. *In-vitro Release Kinetics*

In order to predict the physical mechanism of the Acyclovir *in-vitro* release behavior of all the formulations prepared with different D:P ratios (10:5, 10:6, 10:7, 10:8, 10:9, and 10:10), release data were compared using the following mathematical models [12].

$$W = K_1 t \dots\dots\dots(1)$$

1. Kinetics of First order [13]

$$\ln (100-W) = \ln 100 - K_2 t \dots\dots\dots(2)$$

2. Kinetics of Higuchi [14]

$$W = K_4 t^{1/2} \dots\dots\dots(3)$$

3. Kinetics of Hixson Crowell [12]

$$(100 - W)^{1/3} = 100^{1/3} - K_3 t \dots\dots\dots(4)$$

4. Equations of KorsmeyerPeppas [15]

$$M_t / M_\infty = K_5 t^n \dots\dots\dots(5)$$

Where

W = percent drug release at time t.

$k_1$ - $k_4$  = Constants of release rates, depending on the kinetic model used.



$M_t/M_\infty =$  The fraction of drug released.

$k_5 =$  Constant for integrating geometric and structural properties of tablets.

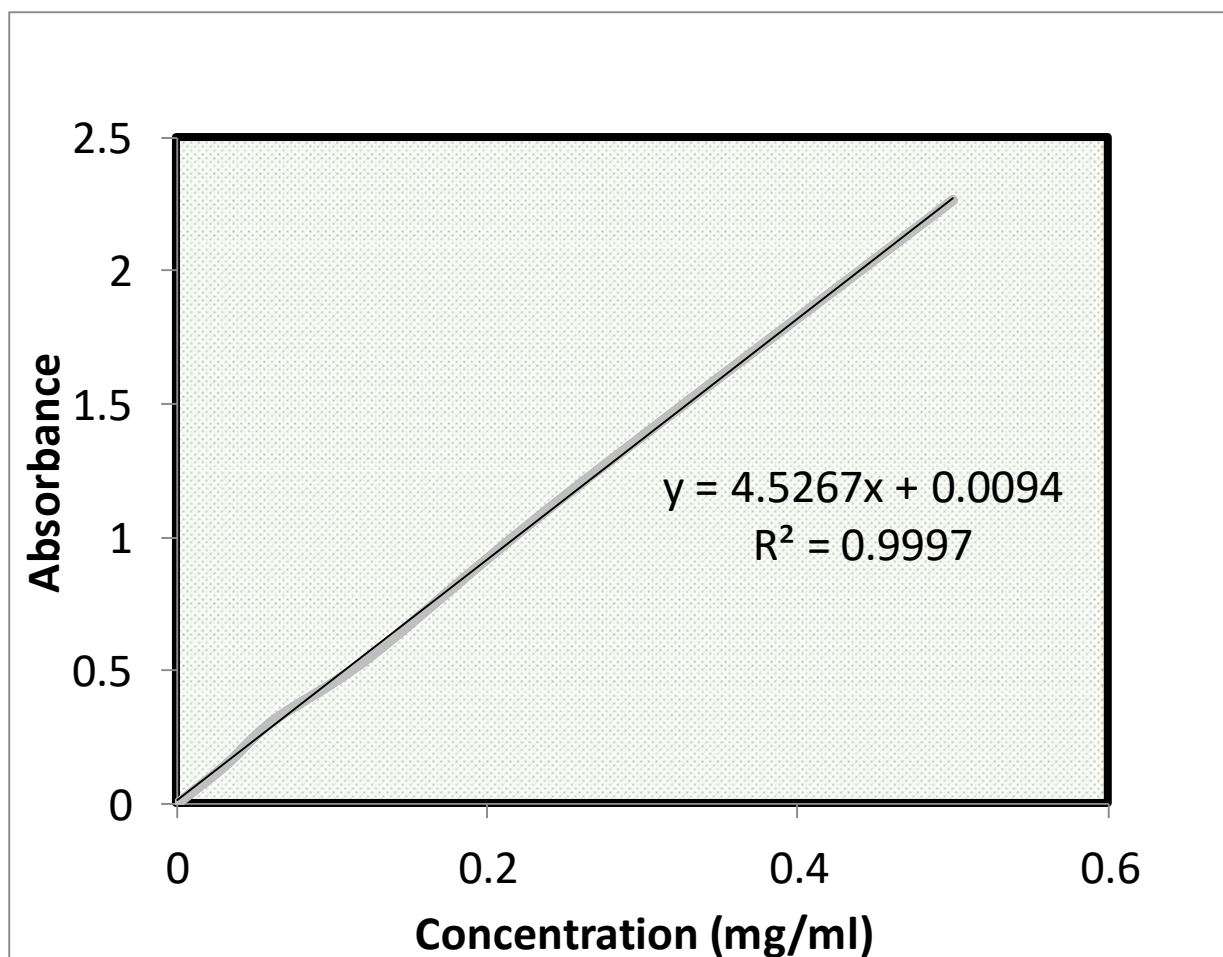
$n =$  diffusion exponent for characterization of drug release transport mechanism

### 3. Results and Discussion

#### 3.1. *Standard Calibration Curve of Acyclovir*

The standard calibration curve of Acyclovir was obtained using the method mentioned in previous section.

Using UV-Visible spectrophotometer, absorbance values of stock solution of Acyclovir and its different dilutions were taken and plotted against its respective concentrations. Standard calibration curve of Acyclovir was constructed using Microsoft Excel and presented in Fig 1 along with equation of regression and ( $R^2$ ) value.

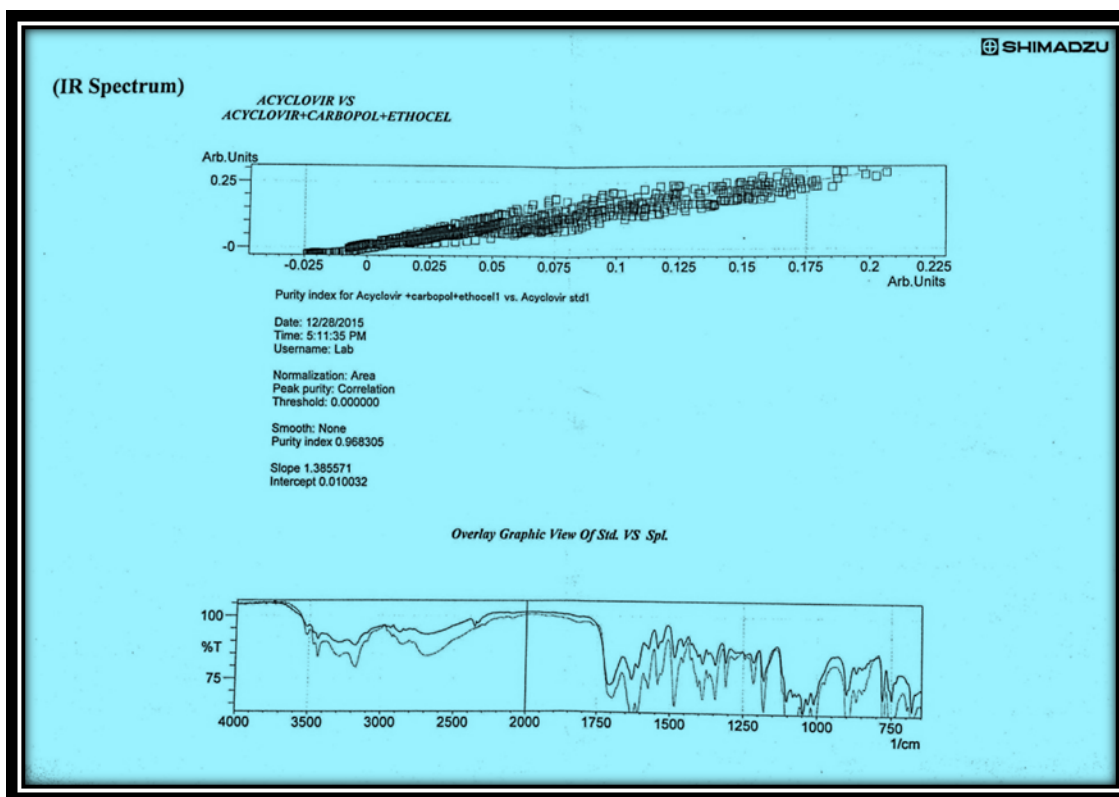


**Figure 1:** Standard calibration curve of Acyclovir  
**Chemical Integrity**

3.2.

For the assessment of any possible chemical interaction between pure drug and used polymer in the formulation, Fourier transform infrared spectroscopy (FTIR) spectra were taken for Acyclovir alone and with its mixture with Carbopol and Ethocel.

The FTIR spectra are illustrated in fig 2. First, the characteristic bands of the polymers and pure drug were observed as shown in fig, the main characteristic bands. The characteristic bands of pure Acyclovir acquired from the spectra of FT-IR were similar to those as documented in literature and shown in fig 2. The graph of pure Acyclovir overlaps on mixture of Acyclovir with polymers. The purity index was found to be 96.68 percent.



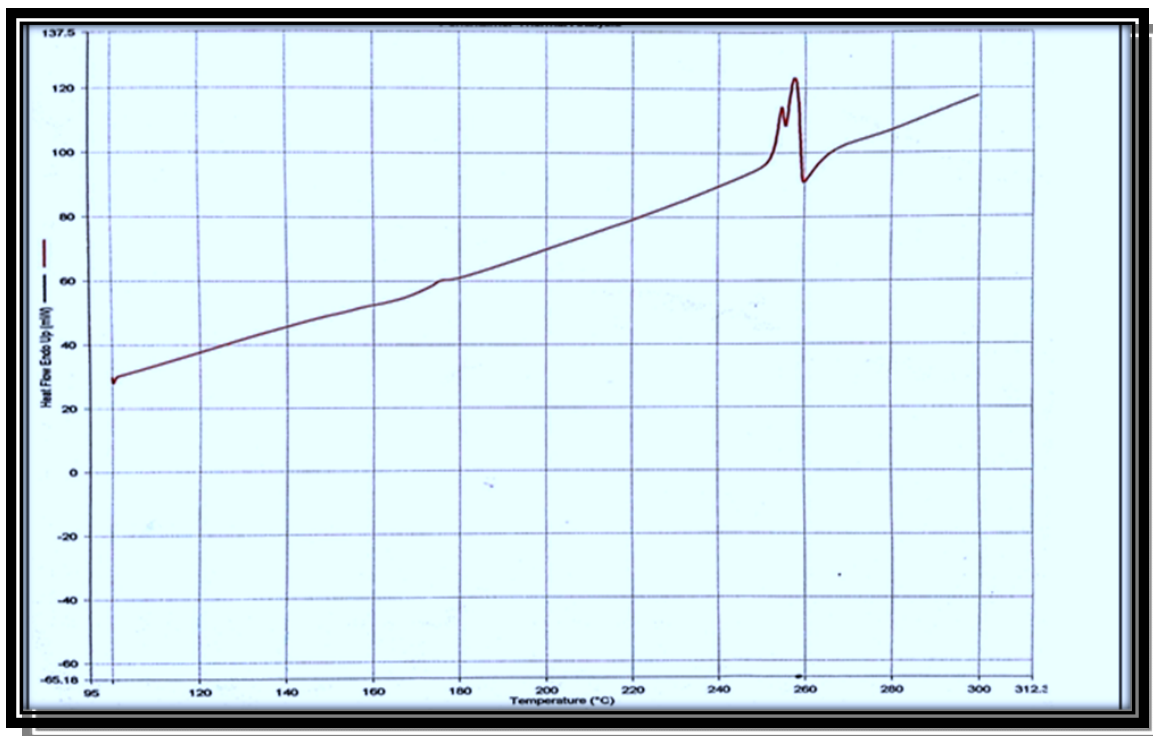
**Figure 2:** FTIR spectra of Acyclovir pure drug and its mixture with polymers

Ethocel-Carbopol represented good candidates for CR tablets of Acyclovir, where the obtained integrity was intact and Acyclovir release was sustained for 24 h. Furthermore, the presented complex did not affect the chemical integrity or stability of the active drug.

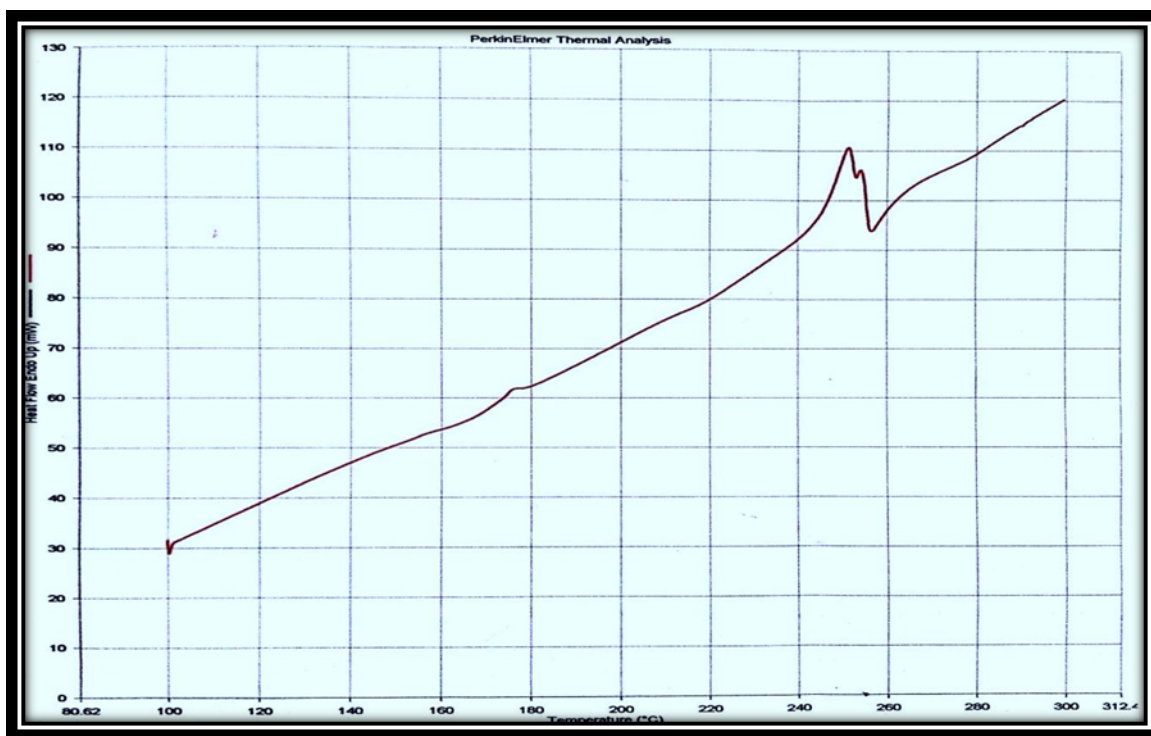
### 3.3. Thermodynamic Behavior of Acyclovir and its mixture with polymer

DSC thermograms of untreated acyclovir, physical mixture of acyclovir with polymers in a ratio 10:5 and 10:10 (optimized acyclovir CR tablets) are shown in Figure 3 and 4 respectively. The thermal graphs of Acyclovir and its mixture ratio at 10:5 and 10:10 were almost similar signifying that they are compatible with each other. The physical mixture of acyclovir and polymers showed the same thermal behavior as the individual components, i.e. melting endotherm at 249 °C. The endothermic peak, representing melting of acyclovir, vanished in the thermogram of acyclovir-encapsulated CR tablets.

These findings are in accordance with previous findings reported by Musumeci et al and Prerak et al [16,17].



*Figure 3: Acyclovir pure drug DSC thermogram*

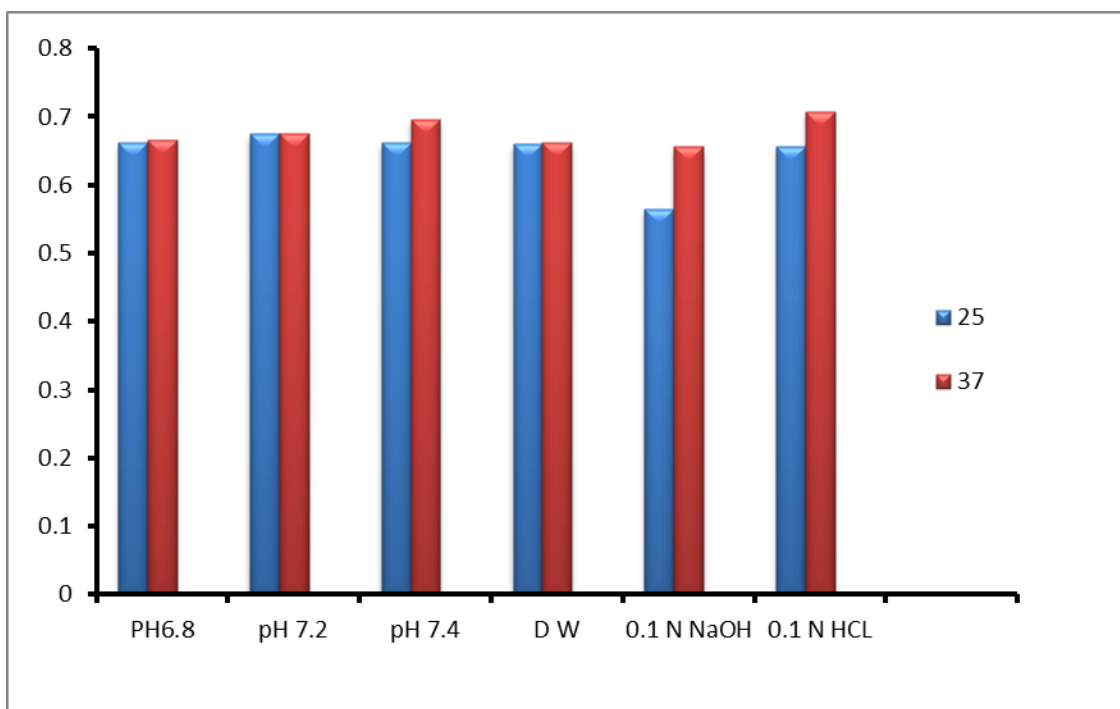


**Figure 4:** *Acyclovir pure drug + Ethocel + Carbopol (10: 10) DSC thermogram*

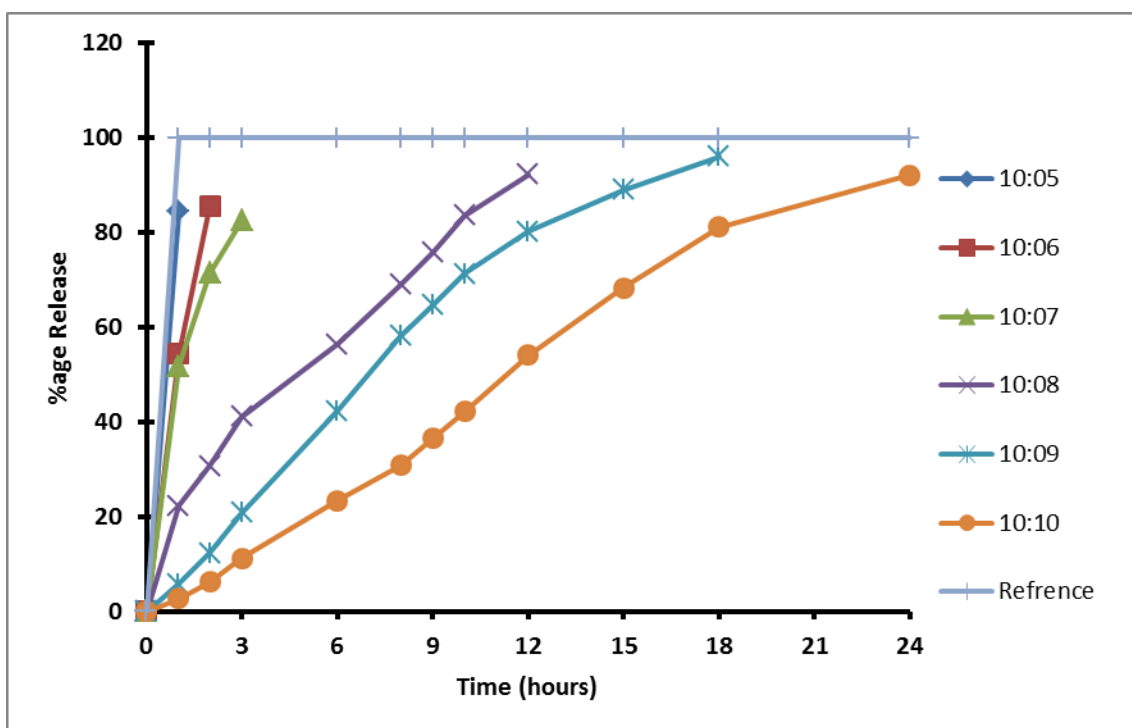
The physical mixture of acyclovir and polymers showed the same thermal behavior as the individual components, indicating that there was no interaction between the drug and the polymer in the solid state. The results suggested that the drug was molecularly dispersed in the polymers matrix and it might exhibit amorphous or disordered crystalline state as reported previously by Prerak et al [17].

### 3.4. *Solubility of Acyclovir*

The results obtained from solubility study are depicted by fig 6. Acyclovir has highest solubility in 0.1 N HCl at 37 °C. Among several phosphate buffers the solubility of Acyclovir was highest at pH 7.4. The least solubility has been observed in 0.1 N NaOH at 25 °C as shown in fig 6.



**Figure 5:** Solubility study results of Acyclovir in different solvents stored at 25 and 37 °C



**Figure 6:** Release profile of Acyclovir with Carbopol and Ethocel at (D:P ratio 10:5, 10:6, 10:7, 10:8, 10:9, 10:10) and from Reference (immediate release formulation)

### 3.5. *Tabletting Parameters Results*

Acyclovir control release tablets were prepared by wet granulation method, at different drug to polymer ratios of 10:5, 10:6, 10:7, 10:8, 10:9, and 10:10. The final formulations were inspected for their different physical characteristics. Tables 2 presented the thickness, hardness and friability, while table 3 shows the disintegration applied to CR tablets of Acyclovir with Carbopol and Ethocel. All the tablets of above mentioned formulations were well-made in look and were having smooth shiny surfaces. As displayed in table 2, the mean thickness of CR tablets of Acyclovir of all formulations, prepared by wet granulation technique with Carbopol and Ethocel were about 5mm which are within the USP range (2-6mm).

**Table 2: Results of Tabletting Parameters of Acyclovir CR tablets prepared by Wet granulation Method**

<b>Formulation code</b>	<b>Hardness (kg/cm<sup>2</sup>)</b>	<b>Thickness (mm)</b>	<b>Friability (%)</b>
<b>F1</b>	12±0.10	5.5 ±0.15	0.51±0.08%
<b>F2</b>	13±0.12	5.5±0.20	0.54±0.1%
<b>F3</b>	14±0.10	5.49±0.17	0.52±0.11%
<b>F4</b>	14±0.15	5.5±0.15	0.53±0.08%
<b>F5</b>	15±0.11	5.48±0.16	0.58±0.13%
<b>F6</b>	16±0.13	5.5±0.11	0.63±0.15%

All values expressed in mean ± SD

**Table 3: Results of Disintegration Test of Acyclovir CR tablets prepared by Wet granulation Method**

<b>Formulation code</b>	<b>D:P Ratio</b>	<b>Disintegration time of 6 Tablets in phosphate Buffer pH 6.8</b>	<b>USP Range</b>
<b>F1</b>	10:5	12±0.09 min.	NMT 45 min.
<b>F2</b>	10:6	12 ±0.12min.	NMT 45 min.
<b>F3</b>	10:7	13±0.15 min.	NMT 45 min.
<b>F4</b>	10:8	10±0.11 min.	NMT 45 min.
<b>F5</b>	10:9	12±0.15 min.	NMT 45 min.
<b>F6</b>	10:10	13±0.15 min.	NMT 45 min.

All values expressed in mean ± SD

The mean hardness of CR tablets of Acyclovir of all formulations with Carbopol and Ethocel, was in the range from 12-16 which were within the USP satisfactory limits i.e. (10-20 kg/cm<sup>2</sup>), the hardness of formulation 10:10 D: P ratio was maximum as compared to rest of formulations due to use of high fraction of polymers.

Disintegration tests were then applied to all formulations as given in table 3. Tablets with Carbopol and Ethocel were disintegrated within 15 minutes. The friability tests were performed after disintegration tests for all formulations of Acyclovir with Carbopol and Ethocel. The results of all formulations were within USP satisfactory friability range, the mean value of friability was less than 0.8%.



### 3.6. Drug Release Studies

As displayed in figure 4 CR Acyclovir tablets formulations prepared by wet granulation method at different drug to polymer ratio of 10:5, 10:6, 10:7, 10:8, 10:9, and 10:10. The formulations of D: P ratio 10: 10 prolong the release of Acyclovir drug to a more extent and the 96% of whole the drug was released in 24 hours. The release from 10: 5 was extended only up to 1 hour and 84.39% drug was released. The second formulation 10:6 extended the release up to 2 hours. The third formulation 10: 7 prolonged the release time to 6 hours. The release of drug was extended up to 12 hours by fourth formulation. From formulation of 10: 9 the release was much slower and extended to 18 hours. Final formulation 10:10 gave us the desired result and release of drug was extended up to 24 hours.

The results of *in vitro* dissolution study of each formulation (D:P ratio 10:10) are taken with the help of USP method 1 according to the procedure mentioned in methodology section. The results of each formulation have been shown individually in figure 6. The rate of the drug release (until 24 hours) tended to decrease with increase amounts of either Carbapol or ethocel. According to literature findings, the slowing effect of both polymers is due to increases in the viscosity of the gel layer around the matrix tablet [18,19]. Both polymers have a affinity of making gel when they come into contact with aqueous layer. So, at high levels, polymer concentrations are increased around the tablet, and so is the viscosity of the outer layer, which results in decreases in the release of the drug, which then subsequently limits the release of the drug from the matrix [18]. Gel creation occurs due to dissociation of the carboxyl groups of Carbapol at a pH above their  $pK_a$  (i.e.,  $6.0 \pm 0.3$ ), which causes uncoiling and the development of molecules due to the

production of an electrostatic repulsive force between the negatively charged carboxyl groups. Uncoiling and expansion of the molecules result in polymer swelling and, consequently, gel is formed, which consists of closely packed swollen particles. With increases in the amount of polymer, this gelling property increases, and thicker gel restrains water penetration, which ultimately reduces the release of the drug. At high levels of both polymers, a considerable fraction of the drug (~16%) remained unreleased until 24 hours, which may result in reductions in the extent of bioavailability significantly. Charyulu et al prepared acyclovir controlled release tablets using HPMC K15M and sustained the release for 10 hrs. Similarly CHAUDHARI et al formulated controlled release tablets of acyclovir using hydrophilic polymer, polyethylene oxide and the maximum sustained action was observed for 12 hrs [20,21]. Acylex<sup>®</sup> by Ferozsons (pvt) Ltd Noshehra, Pakistan was used as a reference drug which gave 100% release after 40 Minutes.

### **3.7. Kinetic Analysis of Drug Release Data**

Kinetic analysis of drug release data was done by using the mathematical models [19]. It was found that the formulation F6 followed zero order release and formulations F1, F2, F3, F4 and F5 followed first order release as shown in table 4. The data of the various models revealed that formulations F1, F2, F3, F4 and F5 followed Higuchi matrix model whereas formulations F6, follows Korsmeyer-Peppas model. In case of formulation F6 the n value for Korsmeyer-Peppas model was found to be in range less than 0.5, which indicates mechanism of drug release by Fickian diffusion whereas in case of formulations F1, F2, F4 and F5 the n value for Korsmeyer

Peppas model was found to be more than 0.5, which indicates mechanism of drug release by non fickian diffusion by those formulations.

**Table 4:** Kinetic models Parameters applied to release profile of CR tablets

S.No	Kinetic model	k <sub>1</sub>	r <sub>1</sub>	k <sub>2</sub>	r <sub>2</sub>	k <sub>3</sub>	r <sub>3</sub>	k <sub>4</sub>	r <sub>4</sub>	k <sub>5</sub>	r <sub>5</sub>	N
1	$W = k_1 t$	1.02	0.21									
2	$(100-w) = \ln 100 - k_2 t$			0.05	0.889							
3	$(100-w)^{1/3} = 100^{1/3} - k_3 t$					0.16	0.897					
4	$W = k_4 t^{1/2}$							2.03	0.975			
5	$M_t / M_\infty = k_5 t^n$									3.13	0.994	0.965

#### 4. Conclusion

Based on the results of these studies, it was concluded that the blend of Ethocel and Cabapol polymers can be used as efficient matrix former to provide controlled release of acyclovir. The formulation F6 can retard the drug release rate up to 24 hours which can lead to OD dose and can enhance patient compliance as the usual dose is QID. In the present work, 1<sup>st</sup> time the attempt has been made, formulating CR tablets of acyclovir using blend of hydrophilic and hydrophobic polymers. It is suggested to perform pharmacokinetic parameters ( $t_{1/2}$ ,  $C_{max}$ ,  $T_{max}$ ) and IVIVC *in-vivo*.

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### **Author contributions**

Faheem Haider carried the research work. Dr Barkat Ali Khan supervised the project. All other co-authors contributed in the provision of resources, data analysis, final editing.

### **Disclosure**

The author reports no conflicts of interest in this work.

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