RESEARCH ARTICLE

Formation and Characterization of Carbopol 971P-PVP Interpolymer complex and its application for sustained delivery of Acyclovir

Avinash H. Hosmani*[1], Yogesh S. Thorat[2], Indrajeet D. Gonjari[3], Amrut B. Karmarkar[4]

[1]Govt. College of Pharmacy, Ratnagiri, Maharashtra, India.
[2]DSTSM's College of Pharmacy, Solapur, Maharashtra, India.
[3]All India Council for Technical Education, New Delhi, India
[4]Institute of Clinical Research, Mumbai, Maharashtra, India.

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ABSTRACT

Complexation between polymers can be productive with the advantage of broadening of application areas, altered physicochemical characteristics, decreased concentration required. The present investigation was aimed to prepare inter-polymer complex between Carbopol 971P and different grades of Poly (vinyl pyrrolidone) such as K25, K30, K90, VA/ S-630. Extension of the idea was to apply the optimized complex for the sustained release of Acyclovir. The study of interaction between polymers and thermotropic properties of polymers was done by FTIR Spectroscopy and Differential Scanning Calorimetry. Water retaining capacity, pH, conductivity, swelling and mucoadhesion were used to compare the physicochemical and pharmaceutical properties of individual polymers and interpolymer complex. Interpolymer complexation of Carbopol 971P was completed between all grades of PVP but the most significant was in case of PVP K90. Complex showed good mucoadhesion and swelling behaviour. Acyclovir was used as model drug to study the sustained release ability of polymer complex. Drug release of Acyclovir from interpolymer complex disc was found to follow Peppas model as best fit model showing a delayed release. Thus interpolymer complexation between Carbopol 971P and PVP was found to alter physicochemical properties of polymers. The novel approach was stable and effective to sustain drug release.

Keywords: Carbopol 971P, Carbomer, PVP, Inter-polymer complex, Acyclovir, Sustained release.

INTRODUCTION

Polymers are the substances of high molecular weight with repeating monomer units widely used in pharmaceutical systems. The chemical reactivity of polymers depends upon chemical nature of their monomer units, but their properties depend upon the way the monomers are put together.[1] Modifications of polymers and their properties is an important technological problem. For realization of this problem, some scientific principles for polymer modification are necessary. The change of structural organization of polymer systems can be used as indicator of polymer modification. The ways to perform polymer modification include interpolymer complexes, protein-polymer conjugates, macromolecular metal complexes and complexes of polymers with low molecular weight compounds.[2] However, use of interpolymer complexation method has wide applications in case of pharmaceutical delivery systems. These include mucoadhesive systems using poly (acrylic acid),[3-5] poloxamer,[4] Poly (vinyl) pyrrolidone;[6] complexation hydrogels using poly(methacrylic acid grafted with poly(ethylene glycol)), (P(MAA-g-EG));[7] controlled drug release;[8,9] nanoparticulates;[10] in situ gelling systems [11] etc.

In particular, use of Carbopol as mucoadhesive polymer is widely accepted. It was used in various interpolymer polymer complexes for controlling drug release.[9-12] Poly(vinyl pyrrolidone) (PVP) was used by Gonjari et al.[13] as mucoadhesive polymer for ophthalmic gels. PVP was used for complexation with various other polymers. Chun et al.[14] studied complexation of PVP and poly (acrylic acid). In another study, PVP was complexed with poly vinyl acetate phthalate.[15]

Complexation between polymers can be studied by measurement of turbidity, pH, and ionic strength as the function of weight ratio of polymer in media,

Address for correspondence

Dr. Avinash H. Hosmani

Govt. College of Pharmacy,
Ratnagiri-415612.
Maharashtra, India.
E-Mail: dr.ahhosmani@gmail.com

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Fourier Transform Infrared Spectroscopy, X-ray diffraction, Nuclear magnetic resonance, etc. [16]

The aim of present research was to investigate interaction between Carbopol 971P, a widely used mucoadhesive polymer and different grades of PVP (K30, K90 and VA/S-630). The interaction between both the polymers was studied by amount of fresh and dried complexes formed, water retaining capacity, apparent density, pH and conductivity. Additionally, the complexes were analyzed by Differential Scanning Calorimetry, Fourier Transform Infrared Spectroscopy, and swelling and adhesion tests.

MATERIALS AND METHODS

Materials

Carbopol 971P was a gift from Noveon (India); PVP (K25, K30, K90, VA/S-630) were gifted by Cipla (India). The molecular weight for PVP grades K25, K30, K90 and VA/S-630 was 30,000; 50,000; 1,000,000 and 58,000 respectively. The chemical structures of Carbopol 971P and PVP were as shown in figure 1.

Preparation of Carbopol 971P and PVP complex

2% aqueous dispersion of Carbopol 971P and PVP K 25 were first prepared. Appropriate amount of aqueous dispersions of Carbopol 971P and PVP were mixed to obtain Carbopol 971P to PVP weight ratio of 1:1, 3:7, and 7:4 (weight fraction of 30%, 50%, and 64% of Carbopol 971P respectively) with total polymer concentrations at 2% by weight in each sample. The polymeric solutions were stirred uniformly for 60 min and filtered through Whatman filter of 45 µ. The residue consisting of Carbopol 971P-PVP complex was collected and weighs to represent the weight of fresh polymer complex (W_f). The complex was dried at 100^{0}C until a constant weight was obtained. The dried complex was ground and sieved through no. 60 mesh sieve, while the filtrate was collected and analyzed further.

Determination of pH and conductivity

The pH and conductivity of Carbopol 971P and PVP (K25, K30, K90 and VA/S-630) mixtures were determined by pH cum conductivity meter (ELCO, Mumbai, India) of cell constant 1cm^{-1} at 25^{0}C using each sample containing 2% of total polymer concentration.

Determination of Apparent density

Pycnometer was used to determine apparent densities of pure polymer dispersions of Carbopol 971P and PVP grades (2% dispersions in water) and filtrates obtained after complexation (1:1 ratios). All studies were done in triplicate.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were obtained using a Perkin-Elmer Spectrum-one FTIR spectrometer (Shelton, CT, USA) spectrometer using KBr disks. The samples of Carbopol 971P, PVP K90 and Carbopol-PVP K90 solid complex (1:1) were previously ground and mixed thoroughly with KBr. The KBr disks were prepared by compressing the powder. The scanning range was kept from 4000-500 cm^{-1} and the accumulations were 4.

Differential Scanning Calorimetry (DSC)

Differential scanning Calorimetry was done by SDT2960 (TA Instruments Inc., USA) was performed to assess thermotropic properties and thermal behaviours of Carbopol 971P, PVP K90 and Carbopol-PVP K90 solid complex (1:1). Samples were placed in aluminium pans and lids at constant heating range of 15^{0}C/min, covering temperature range to 300^{0}C. Nitrogen was used as purge through DSC cell.

Preparation of polymer discs for swelling and bioadhesion studies

The discs (250 mg) of 13mm diameter were prepared using Tablet press (Technosearch Industries Ltd, Mumbai, India) at a pressure 10 kN/cm^2 for 1min. The discs were prepared by Carbopol 971P-PVP K90 solid complex or 1:1 physical mixtures of Carbopol 971P to PVP.

Swelling studies

The Carbopol 971P-PVP K90 disc was submerged in Petri dish containing 80 ml of phosphate buffer pH 7.4. Diameter was measured at different time intervals over 60 hr with vernier calliper (Mettler) at 25^{0}C.

In vitro mucoadhesion evaluations

The mucoadhesive force was determined by method given by Choi HG, et al. [17] A section of gastric mucosa was cut from the sheep's stomach and instantly fixed with mucosal side out onto each glass vial using rubber band. The vials with mucosa were stored at 37^0C for 5 min. Then next vial with a section of mucosa was connected to the balance in inverted position while first vial was placed on a height adjustable pan. The polymer disc was placed onto the gastric mucosa of first vial. Then the height of second vial was so adjusted that the mucosal surfaces of both vials come in intimate contact. Ten minutes contact time was given. Then weight was kept rising in the pan until vials get detached. Mucoadhesive force was the minimum weight required to detach two vials. The mucosa was changed for each measurement.

In vitro dissolution studies

Drug release studies were performed using Acyclovir as model drug. The extended-release matrix tablets with a total weight of 250 mg were prepared using a mixture of Acyclovir and Carbopol 971P-PVP K90 complex at 1:1. The tablets were prepared using Tablet press (Technosearch Industries Ltd, Mumbai, India) by applying10 kN/cm^2 for 1min with a 13 mm diameter. The dissolution studies were performed using USP Apparatus II dissolution tester (LabIndia, India). Tablets were placed in dissolution vessel containing 900 ml pH 1.2 HCl maintained at 37±0.5^{0}C and stirred with paddle at 100 rpm. Samples were collected periodically and replaced with dissolution medium. After filtration through Whatman filter paper 41, concentration of Acyclovir was determined spectrophotometrically at 256 nm (Shimadzu 1700 UV-Vis Spectrophotometer). [18, 19]

RESULTS AND DISCUSSION

The amount of fresh and solid complexes obtained, water retaining capacity, conductivity, adhesion properties, and the swelling property of physical mixture were directly correlated to Carbopol concentration. water retaining capacity were positively correlated with the molecular weight and viscosity type of PVP, while the solid complex and apparent density of the complex filtrate were negatively associated with the molecular weight and viscosity type of PVP.

Water retaining capacity

The maximum interpolymer complexation between Carbopol 971P and PVP was at a ratio of 1:1. The preparation of complexes of Carbopol 971P and PVP (K25, K30, K90, VA/S-630) grades showed that maximum complex occurred with Carbopol 971P-PVP K90 at a ratio 1:1. The amount of fresh and dried complexes greater with an increase in Carbopol 971P concentration up to weight ratio 1:1 (50% Carbopol 971P) but decreased with a further increase in Carbopol 971P concentration. (Table 1)

The amount of fresh Carbopol 971P-PVP complexes obtained was highest for PVP K90, followed by VA / S630, K30, and K25. The PVP K90 which has higher molecular weight and viscosity played an important role in polymer complexation process. The concentration of Carbopol 971P determined extent of complexation. The 50% concentration showed greater amount of complexes. Water retaining capacity of VA / S630 was found to be greater than PVP K30 though they are having similar viscosity ranges and molecular weights. This might be due to presence of vinyl acetate in the VA / S630 grade.

Effect on apparent densities

As depicted in Table 2, the apparent density of filtrates of Carbopol 971P- PVP K90 complex was lowest among all the filtrates. The apparent density of filtrates of Carbopol-PVP (K25, K 30, VA /S630) complex was highest than their respective PVP solution.

Effect on pH

Aqueous dispersion of Carbopol 971P exhibited pH values between 2.8 to 3.2, depending on its concentration. Generally increase the concentration of Carbopol 971P decreased pH of all the complexes (Fig. 2). This might be due to presence of carboxyl functionalities in the structure of Carbopol. All the

Carbopol-PVP complexes were insoluble in acidic aqueous solution. Decomplexation occurs in basic media (pH 8), which was adjusted with 2 M NaOH.

Effect on Conductivity

Conductivity is the function of the movement and concentration of ions. Hence it can be used as an indicator of the degree of complexation between polymers in aqueous solution. All grades of PVP interacted with Carbopol 971P and conductivity was positively correlated with concentration of Carbopol 971P (Fig. 3). Increase in conductivity was observed with Carbopol 971P-PVP K90 complex when the Carbopol concentration was increased from 50 to 90%, while below 50% of Carbopol, there was only a gradual increase similar to the rest of the Carbopol 971P- PVP complexes. This indicates that at lower Carbopol 971P concentration, the insoluble complex was surrounded by poorly conducting PVP solution. At a higher Carbopol concentration, a larger amount of flocculated insoluble complexes leads to increase the conductivity.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies (Fig. 4) revealed characteristic -OH peaks at 3110 cm^{-1} and 3400 cm^{-1} for Carbopol 971P and PVP K90 respectively. These peaks were absent in the Carbopol 971P- PVP K90 complex. The carbonyl groups were observed at 1700 and 1720 cm^{-1} Carbopol 971P and PVP K90 respectively. These peaks in the complex were found less sharp.

Differential Scanning Calorimetry (DSC)

In the DSC thermogram of Carbopol 971P (Fig. 5), glass transition temperature *(T_g)* was observed near the range of 120-140 ^{0}C. Decomposition of Carbopol 971P was observed near 280-300 ^{0}C where Carbopol melted and decomposed sequentially [17, 20, 21]. The endothermic peak at 80-100 ^{0}C was due to physically bound water. Also in case of PVP K90, sharp endothermic peak at 80-100 ^{0}C was observed indicating presence of bound water or moisture. As reported by Hancock et al [22], T_g of PVP was 177 ^{0}C. But no glass transition temperature *(T_g)* was observed in the sample of PVP. Only less endothermic peak at 80-100^{0}C in case of complex indicate less moisture or physically bound water.

Swelling study

The polymer complex discs showed diameter of 4.1$\pm$0.2 cm after 24 hr. The amount of polymer directly affects the solvent transfer rate and hence swelling index also increases with increasing Carbopol 971P concentration. This may be due to higher water sorption capacity of carbomers. It also indicates sustained release behaviour of polymer complex.

In vitro mucoadhesion study

Various grades of Carbopol have been used for their bioadhesive properties. [23] The PVP has been widely used as a binder but it also possesses certain mucoadhesivity. [13] Carbopol 971P and PVP K90 complex showed mucoadhesion of 837.527 $\pm$ 18.23 dynes / cm^2. The reason for higher bioadhesion is attributed to higher water sorption capacity of Carbopol 971P. Bioadhesivity of interpolymer complex discs enhances contact time with mucosa and increases efficacy of the dosage form by sustaining drug release.

In vitro drug release

Dissolution is critical character of pharmaceutical dosage forms. Fig. 6 shows dissolution profile of acyclovir from polymer discs of pure polymers and complexes. The Carbopol has been used previously for sustained and controlled release. [25] It was found that acyclovir release was retarded in case of complex whereas, release from PVP K90 discs was found to be faster. Carbopol discs showed release in between them. It is postulated that lightly cross- linked polymer Carbopol 971P has a “fishnet” gel structure upon hydration.[26] Because there are few cross-linking sites to constrain the polymer; it opens up easily at low concentration. Consequently, when PVP K 90 forms a complex with Carbopol 971 P, the interstitial spaces between the swollen gel particles are eliminated, and there is no significant difference between micro and macro viscosity. This homogenous gel structure provides significant resistance to the diffusing molecules. Less porous is the polymer

complexes due to which very few channels are formed in the compact, hence retard the drug release. The drug diffuses into the gel particles and it has relatively less channels to exhibit drug hence, swelling of the gel matrix along with diffusion is the rate controlling step. Thus drug release shows better drug retardation from the complex. Dissolution profile when subjected to model fitting (Table 3, Fig.6) showed "Peppas" model as best fit model. This is due to previously proved fact depending on R^2 value obtained from model fitting. [27] Korsmeyer-Peppas release exponent 'n' was also studied. The 'n' values for complexes were found to be 0.7272. This indicates anomalous transport.

Table 1: Amount of complexes collected from 400 gm of 2% polymeric mixtures

Complex with various Grades of PVP	Carbopol 971P concentration (%)	Amount of Fresh complex ± SD (gm)	Amount of dried complex± SD (gm)
PVP K25	50	14.3 ± 1.52	3.61± 1.12
PVP K30	30	18.50 ± 1.23	4.12 ± 0.89
	50	32.08 ±0.43	5.59 ± 0.93
	64	21.64 ± 1.21	4.48 ± 0.86
PVP K90	30	135.11±3.34	3.48 ±0.91
	50	1180.08±4.32	5.69 ± 1.21
	64	240.3 ± 5.32	7.18 ±1.32
PVP VA/ S630	50	62.18 ± 2.12	5.62 ± 1.25

CONCLUSION

Interpolymer complexation between Carbopol 971P and various grades of PVP was found to alter physicochemical properties of these polymers. Yield of complex was found to be good in case of complex with PVP 90. FTIR and DSC studies showed stability of the complex. The complex showed good mucoadhesion and swelling. Complex showed to sustain release of Acyclovir. The dissolution profile showed Peppas model as best model. Hence this novel approach was found to be more appropriate to sustain release of drug.

Table 2: Apparent density as a function of different complexes

Polymer filtrates	Apparent density ± SD
Carbopol 971P	0.450 ± 0.02
PVP	1.015 ± 0.03
Carbopol 971P-PVP K25 complex	1.067± 0.01
Carbopol 971P-PVP K30 complex	1.063± 0.02
Carbopol 971P-PVP K90 complex	1.021± 0.02
Carbopol 971P-PVP VA/S630 complex	1.086± 0.03

Table 3: Release kinetics of Acyclovir from pure polymer and complex discs

Discs of polymer containing Acyclovir	Zero order kinetics (R^2)	First order kinetics (R^2)	Matrix model (R^2)	Peppas model (R^2)	Hixon-Crowell model (R^2)	Korsmeyer-Peppas release exponent (n)
PVP 90	0.6880	0.8867	0.9745	0.9932	0.9747	0.3492
Carbopol 971P	0.9011	0.9958	0.9952	0.9981	0.9994	0.5528
Complex	0.9778	0.9981	0.9749	0.9995	0.9976	0.7272

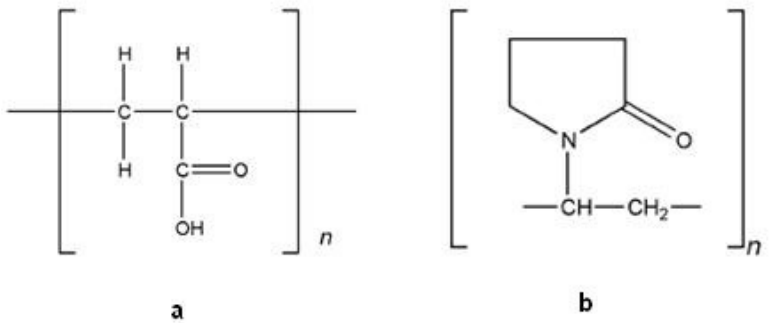

Figure 1: Chemical Structures of Carbopol (a) and Polyvinyl pyrrolidone (b)

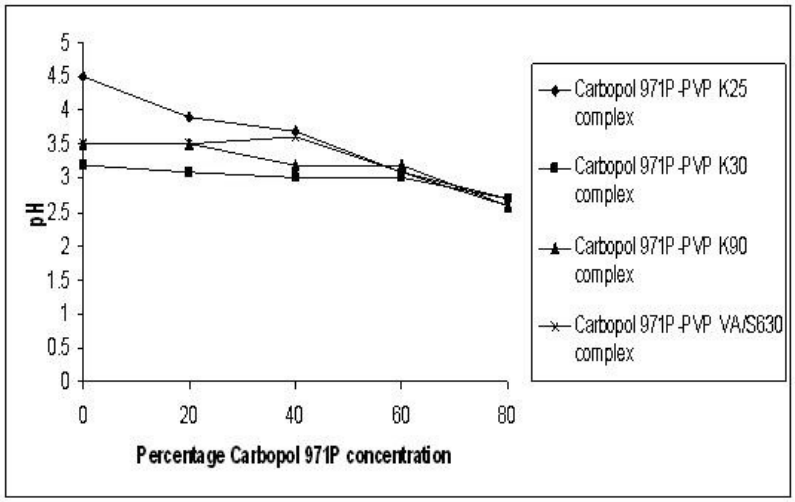

Figure 2: pH as a function of different complexes

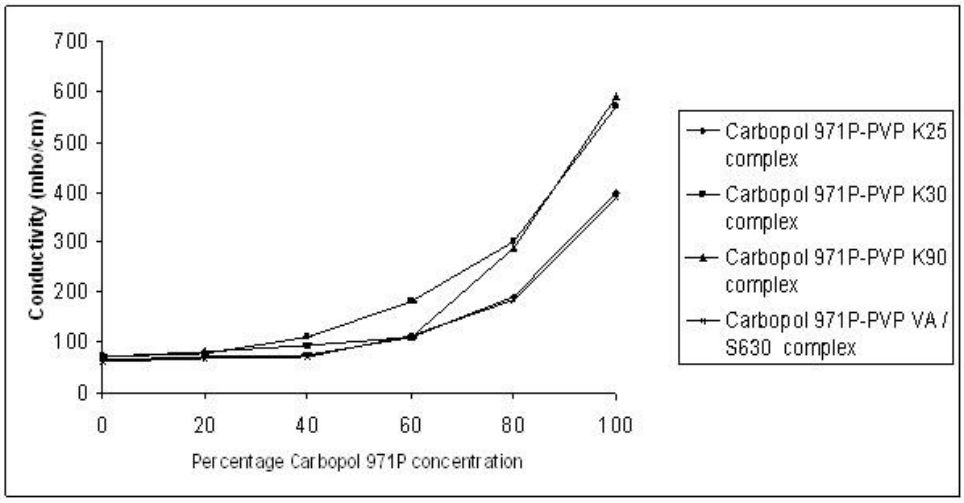

Figure 3: Conductivity as function of Carbopol 971P – PVP complexes

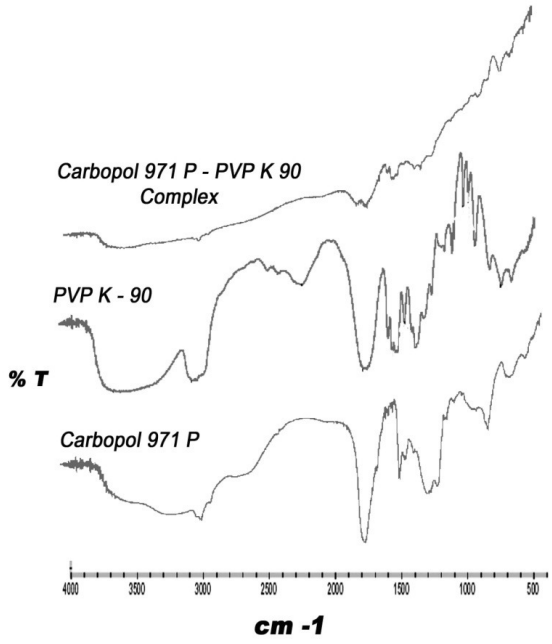

Figure 4: FTIR Spectra of pure polymers and complex

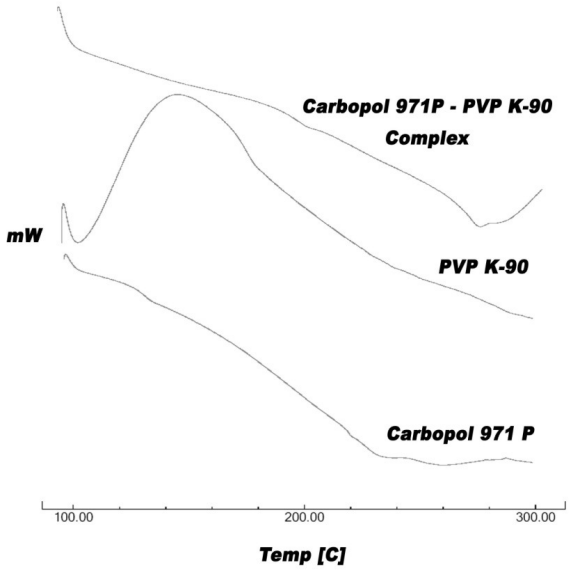

Figure 5: DSC thermograms of pure polymers and complex

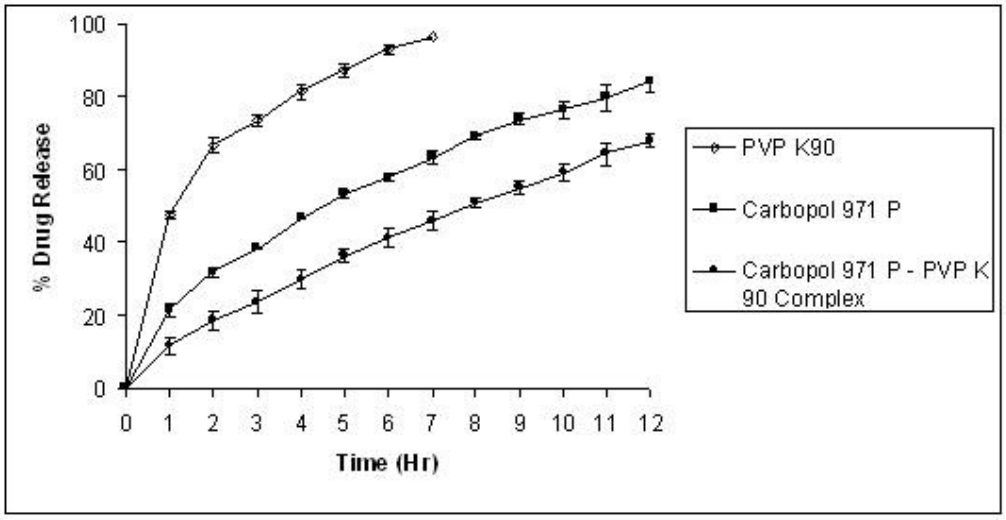

Figure 6: Dissolution profile of Acyclovir from pure polymers and complex

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