RESEARCH ARTICLE

Preparation and evaluation of polyelectrolyte complexes for oral controlled drug delivery

L Srinivas, K V Ramana Murthy[1]

Raghu College of Pharmacy, Dakamarri, Bheemunipatnam, Visakhapatnam 531 162, [1]University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam 530 003, A.P., India

The electrostatic interaction between oppositely charged polyelectrolytes leads to formation of insoluble polyelectrolyte complexes in aqueous medium. The polyelectrolyte complexes formed between a polyacid and a polybase are little affected by the pH variation of the dissolution medium. In the present study attempts were made to prepare polyelectrolyte complexes of polyvinyl pyrrolidone (polybase) and carbopol (polyacid) into which diclofenac sodium is incorporated and studied for its controlled release. The polyelectrolyte complexation was evaluated by pH, conductivity, Fourier transformed infrared spectroscopy, and X-ray difractometry. The dried polyelectrolyte complexes were also evaluated for micromeritic properties and drug release kinetics. Selected PECs were compressed into tablets and compared with commercial SR product for drug release. The tablets showed comparable results with commercial SR product following zero-order release, and drug release is by erosion as well as the diffusion mechanism. Promising results were obtained suggesting the application of these polyelectrolyte complexes in the design of controlled release systems.

Key words: *Carbopol, diclofenac sodium, polyelectrolyte complexes, polyvinyl pyrrolidone, poly ions*

INTRODUCTION

Polyelectrolyte complexes (PECs) are the association complexes formed between two oppositely charged particles (e.g. polymer–polymer, polymer–drug, polymer–drug–polymer). These are formed due to electrostatic interaction between oppositely charged polyions. This avoids the use of chemical crosslinking agents, thereby reducing the possible toxicity and other undesirable effects of the reagents. The polyelectrolyte complexes formed between a polyacid and polybase are little affected by the pH variation of the dissolution medium. This concept of complexation, between DNA and chitosan,[1] has extensively been studied in the development of delivery vehicle for gene therapy and oral vaccination.

The occurrences of charge–charge interactions between ionic polymers and drugs were considered to be a negative event when the ionic polymers are used as excipients in pharmaceutical formulations. In these systems release of drugs may be strongly affected by the occurrence of charge–charge interactions. However, in recent years these negative events of polymer–drug and polymer–polymer interactions have been exploited positively for controlled drug release.[2,3]

Many researchers extensively studied on the properties of the polyelectrolytes[4] and on the formation of polyelectrolyte complexes.[5-7] The formation process of polyelectrolyte complexes may be divided into three main classes (a) primary complex formation; (b) formation process within intracomplexes; and (c) intercomplex aggregation process.[8] The intermolecular forces responsible for formation of complexes are either covalent or coordinated bonds or van der Waals forces of dispersion or ion–dipole or dipole–dipole interactions. Several factors like ion site, charge density, polyelectrolyte concentration, pH, ionic strength, solvents, and temperature affect the formation of PECs.

Polyelectrolyte complexes have gained much attention in the past few years because of their potential applications. These can be used as membranes,[9-11] for coating on films and fibers,[12] for isolation and fractionation of proteins,[13,14] for isolation of nucleic acid,[15-17] for binding pharmaceutical products,[18] as supports for catalyst,[19] and for preparation of microcapsules for drug delivery.[20,21]

Multiple-charged macromolecular compounds with ions of opposite charge precipitate from aqueous solutions

Address for correspondence:
Dr. L Srinivas, Raghu College of Pharmacy, Dakamarri, Bheemunipatnam, Visakhapatnam 531 162, A.P. India.
E-mail: lsrinivas2001@yahoo.com

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depending on the charge distribution and the molecular weight of the final product. In this case, the higher molecular weight compound displaces low molecular weight ions of the same charge. The polyelectrolyte complexes are composed of a macromolecular multiple-charged component of one polarity and many low molecular weight ions of the other polarity or two macromolecular partners with different polarity.

The active substance can be incorporated in to the PECs by four ways.[22] In the first case, the active substance will be entrapped from the solution during precipitation of the complex. The active substance will absorb from the solution and gets incorporated into the already formed complex on contact in the second case. In the third case, the active substance may chemically bond to at least one complex partner and precipitates during complexation. In the last case, the active compound itself may act as a polyion and form a polyelectrolyte complex. The active substance from these PECs will be released either by solution equilibration or by the ion exchange mechanism or by the charge interaction and slow decomplexation as well as breakdown and dissolution of the complex.

The present study is planned for the application of the polyelectrolyte complexation technique in the preparation of microparticles of diclofenac sodium (sparingly soluble drug). Diclofenac sodium is having short biological half-life[23] associated with gastrointestinal disturbances and other adverse effects.[24,25] Administration of the drug in controlled release dosage forms will prolong the duration of action and may minimize the side effects. Though the drug is sparingly soluble in water its solubility increases in alkaline pH and the design of controlled release formulations may become critical. Pair of oppositely charged polyelectrolytes namely carbopol (polyacid) and PVP (poly amide), which are having the tendency for interpolymer complexation, are chosen for the preparation of polyelectrolyte complexes.

MATERIALS AND METHODS

Diclofenac Sodium I.P, was a gift sample obtained from M/s. Aurobindo Pharma Ltd., Carbopol 934P (polyacrylic acid cross-linked with allyl sucrose) obtained from M/s. Ajantha Pharma Ltd., poly vinyl pyrrolidone (PVP K90) purchased from Loba Chem., hydroxy propyl methyl cellulose (HPMC K100 M, Viscosity 100 000 cps) obtained from M/s. Dr. Reddys Laboratories Ltd., talc purchased from S.D. Fine Chemicals, Voveran SR® 100 mg (B.No: 34094V) is a product of Novartis India Ltd. All other reagents and chemicals used were of analytical grade or pharmacopoeial grade and used as obtained.

Investigation of association between the polyelectrolytes

In the formation of polyelectrolyte complex between oppositely charged polyelectrolytes, various parameters such as colloid ratio, pH, and ionic strength play an important role to achieve maximum yield. Hence, optimum conditions required to form a polyelectrolyte complex should be predicted. The effect of various process variables like polymer mixing ratio, pH and ionic strength on the formation of the polyelectrolyte complex as expressed by the solid content of complex formed (dry complex yield) was studied.

pH and conductivity study

The change in the pH and conductivity with respect to the addition of polyions at various mixture weight ratios was determined by using pH meter (Systronics, Model: 361) and conductivity meter (Systronics, Model: 360) with cell constant 0.01 cm^{-1} at 25°C, respectively. In all the cases, 0.1% w/v stock solutions of diclofenac sodium, PVP, and carbopol were prepared for the study.

Effect of polymers mixing ratio on the formation of polyelectrolyte complex

The effect of polymer mixing ratio on the formation of polyelectrolyte complexes was studied by estimation of dry complex weight when the polymers were mixed at different weight ratios. 100 ml of 1% w/v aqueous solution of CP was taken in a 250 ml conical flask. To each flask 20, 25, 33, 50, and 100.0 ml of 1% w/v aqueous solutions of PVP were added respectively to obtain a weight ratio of 5:1, 4:1, 3:1, 2:1 and 1:1of CP: PVP, respectively. Similarly, to 100 ml 1% w/v aqueous solution of PVP, 1% CP solution was added to get weight ratio of 5:1, 4:1, 3:1, 2:1, and 1:1 of PVP:CP, respectively. The flasks were agitated on a vortex mixer for 15 min and kept aside for 1 h. The pH of these systems was determined. There was a precipitation of the complex of the CP-PVP complex. The pH of the final systems was determined by using the pH meter. The complexes were centrifuged at 2000 rpm for 10 min (Remi Research Centrifuge, Type R-24 with fixed angle head). The supernatant was decanted and the precipitate was dried at 60°C to constant weight and the yield of the polyelectrolyte complex formed was calculated.

Effect of pH on the formation of polyelectrolyte complex

The yield of the polyelectrolyte complexes were determined at different pH values of 1-7 by keeping constant CP:PVP weight ratio of 1:1. The pH of the CP solutions were adjusted to values ranging from 1 to 7 by using dilute hydrochloric acid or sodium hydroxide, to which 1% w/v PVP solution was added and the yield was calculated.

Effect of ionic strength on formation of polyelectrolyte complex

The effect of ionic strength in the range of (0-100 mM) on the formation of the complex between the polymers was studied by maintaining the weight ratio of 1:1 of CP and PVP. The above-described procedure is used for the calculation of the yield.

Preparation of PEC

The degree of complexation between carbopol and PVP was studied by considering their weight ratios. This study showed maximum yield of complex between carbopol and

PVP at the weight ratio of 1:1, and hence further studies on the incorporation of diclofenac sodium in these complexes was done at 1:1 weight ratios of carbopol and PVP. The PECs were prepared at drug, carbopol, and PVP ratio of 80:10:10 (DPC-80), 60:20:20 (DPC-60), 50:25:25 (DPC-50), and 40:30:30 (DPC-40). In the preparation of PECs, 0.5% w/v aqueous stock dispersions of Carbopol 934P and PVP K90 were first prepared. An appropriate quantity of carbopol solution was kept for stirring at 300 rpm. A Remi medium duty stirrer with speed meter (model RQT–125) was used for stirring. Appropriate quantity of PVP solution was taken and diclofenac sodium was dissolved in it. This solution was added slowly to carbopol solution while stirring. The stirring continued for 1 h. This solution was centrifuged and the settled complex was collected, washed thoroughly with water, and dried at 80°C for 6 h. The dried mass obtained was crushed and shifted through mesh #20. These shifted particles were further screened for size distribution.

Micromeritic and flow properties of PECs

The particle size analysis of all the ratios of prepared PECs was done by sieve analysis using a set of standard sieves of sieve numbers #20, #30, #40, #60, #80, #100 and the amount retained on each sieve was determined. The static angle of repose (θ) was measured according to the fixed funnel and the free standing cone method.[26] A funnel with the end of the stem cut perpendicular to its axis of symmetry is secured with its tip 2 cm above a graph paper placed on a flat horizontal surface. Powder is carefully poured through the funnel until the apex of the cone thus formed just reaches the tip of the funnel. The mean diameter of the base of the powder cone was determined and the tangent of the angle of repose was obtained.

Compressibility on taping[26] was measured with a sample of 25 g placed in a 100 ml graduated cylinder and the occupied volume (V_0) was determined. After 500 taps, occupied volume was determined (V). From these data, compressibility index (CI) was calculated by using the following formula:

$$CI = \frac{V_0 - V}{V_0} \times 100$$

FTIR spectroscopy

The pure drug diclofenac sodium, Carbopol 934P, PVP K90, and the polyelectrolyte complex of diclofenac sodium (DPC-60) samples were analyzed for the determination of complex formation by Fourier Transformed Infrared Spectroscopic (FTIR, make Perkin Elmer) studies. The IR spectra were done against the KBr background.

X-ray diffraction

The powder X-ray diffraction patterns of pure diclofenac sodium, Carbopol 934P, PVP K90, and the polyelectrolyte complex of diclofenac sodium (DPC 60) were recorded by using an automated Siemens D/5000. The samples were irradiated with monochromatized Cu Kα radiation and analyzed between 2 angles of 30 to 300. The voltages, current, and time per step used were 30 Kv, 20 mA, and 0.5 s, respectively.

Preparation of diclofenac sodium tablets

Diclofenac sodium tablets were prepared using the selected ratios of PECs passed through mesh #20, by the direct compression technique as per the formulae given in Table 1.

Weighed quantities of the ingredients were taken and blended for 10 min and compressed by using rotary tablet compression machine (M/s. Cadmach, 16 station) with 8.0 mm round concave punches. Each tablet contained 100 mg of diclofenac sodium.

Standard physical test of tablets

The physical properties the tablets were studied by subjected for the following tests. Friability[26] (F) was determined by weighing ten tablets after dusting with a camel's hair brush, placing them in Roche-friability tester and they were subjected to 100 falls of 6 inches height (25 rpm for 4 min). After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated.

Hardness was determined by taking six tablets from each formulation, placing one tablet between the jaws of stokes-Monsanto hardness tester and noting the applied pressure (kg/cm^2) for crushing the tablet. Average of six tablet values was taken. Weight uniformity[27] was determined by weighing 20 tablets, individually, taking the average weight, and calculating the percentage deviation of each tablet with respect to average weight.

Drug content estimation

Accurately weighed 100 mg of the PEC powder and transferred into a 100 ml volumetric flask. 5 ml of 5N sodium

Table 1: Formulae of the prepared diclofenac sodium tablets

Ingredient	Quantity per tablet (mg)				
	DPCT80	DPCT60	DPCT60H20	DPCT60H40	DPCT80H20
DPC-80	125*	-	-	-	125*
DPC-60	-	167*	167*	167*	-
HPMC K100M	-	-	20	40	20
Talc	10	10	10	10	10
Total	135	177	197	117	155

*Equivalent weight of PEC containing 100 mg of diclofenac sodium

hydroxide solution was added and sonicated for 15 min. 50 ml of phosphate buffer of pH 7.4 was added to this solution and vigorously shaken for 15 min and made up to volume with buffer. The resulted solution was filtered through 0.45 μm filter paper and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at 275 nm. The drug loading efficiency of the prepared PECs was calculated by using the following formula.

$$\text{Drug loading efficiency} = \left(\frac{\text{Practical amount of drug loaded}}{\text{Theoretical amount of drug loaded}} \right) \times 100$$

Drug content of the diclofenac sodium tablets prepared was estimated by randomly taking ten tablets from each batch and then powdered. The drug content was estimated in the similar manner as discussed above.

Dissolution studies

In vitro dissolution studies were carried out in 900 ml of alkaline phosphate buffer of pH 7.4[28] using USP XXIV type-II (Paddle) dissolution rate test apparatus (model DISSO 2000, M/S Labindia). Sample equivalent to 100 mg of diclofenac sodium, a speed of 50 rpm, and a temperature of 37±1°C were used in each test. A 5 ml aliquot was withdrawn at different time intervals, filtered, and replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted whenever necessary and assayed for diclofenac sodium by measuring absorbance at 275 nm. All the dissolution experiments were conducted in triplicate and the mean values were reported. The dissolution studies were carried for the pure diclofenac sodium and the prepared PECs of #30/40 mesh size. The dissolution studies were also conducted for the prepared diclofenac sodium tablets using the above-mentioned test conditions. Commercial diclofenac sodium sustained release tablet Voveran SR® was also evaluated for dissolution for comparison.

RESULTS AND DISCUSSION

pH and conductivity study

Poly ions posses certain charge when they are present in the aqueous solution. Oppositely charged polyions form an insoluble polyelectrolyte complex in the aqueous medium. There is a possible change in the charge that may occur when the polyelectrolytes interact and form complexes. These interactions and the formation of PECs can be well judged by pH and conductivity studies. In the present study, the polyelectrolytes in solution exhibited various pH and conductivity profiles [Figure 1] when they interact with each other. In the case of carbopol and PVP, when PVP solution was added to carbopol solution, the conductivity decreased gradually (from 46.6 μs to 16.5 μs) and a sharp fall in conductivity (29.6 μs to 24.8μs) was observed during complex formation. Though there was a change in conductivity, very little change was observed in the case of pH (3.96 to 4.20). When carbopol solution was added to the solution of diclofenac sodium and PVP (1:1), the conductivity decreased from 108 μs to 43.0 μs and a sudden change in conductivity (from 91.0μs to 77.3μs) was observed during complexation. The pH was little affected. The pH changed from 6.29 to 5.48. Thus, the pH and conductivity studies clearly indicated the formation of polyelectrolyte complex between Carbopol, PVP K90, and diclofenac sodium.

Effect of polymers mixing ratio on the formation of polyelectrolyte complex

The effect of CP and PVP mixing ratio on the polyelectrolyte complex yield and the respective pH of the final aqueous mixtures are given in Table 2.

As the CP to PVP weight ratio increased, the polyelectrolyte complex yield increased. The same increase in yield was observed when the PVP to CP weight ratio was increased. The maximum polyelectrolyte complex was found to be formed at 1:1 weight ratio of CP:PVP. Hence, this weight ratio of CP to PVP (1:1) was selected for further studies. The pH increased as the CP to PVP weight ratio increased and the pH decreased when PVP to CP weight ratio increased. The pH of 1:1 weight ratio CP:PVP complex was found to be 4.2. This may be due to the interaction of the two polymers.

Effect of pH on the formation of polyelectrolyte complex

Polyelectrolyte complexation is a pH-sensitive process, since the charge and charge density of the polymers vary with pH. At pH values, where the charges are no longer balanced, a reduction in the interaction between the polymers causes a reduction in the complex yield.

The polyelectrolyte complex yield between CP and PVP at different pH ranges was studied. CP is a polyacid and the pH of 1% w/v aqueous solution was found to be in the range of 2.8 to 3.0. The pH of 1% w/v PVP aqueous solution was found to be 4.5 to 4.9. The results of the study are given in Table 3.

Table 2: Effect of polymer mixing ratio on the yield of CP-PVP complex

CP: PVP	% Dry polyelectrolyte complex yield (mean ± s.d.)	pH of the final solution
5:1	28.33±2.58	3.19
4:1	40.25±1.29	3.22
3:1	55.48±3.84	3.27
2:1	62.58±2.72	3.59
1:1	82.75±1.52	4.20
1:2	56.36±3.66	4.33
1:3	42.77±2.98	4.35
1:4	30.18±1.45	4.39
1:5	27.14±3.22	4.90

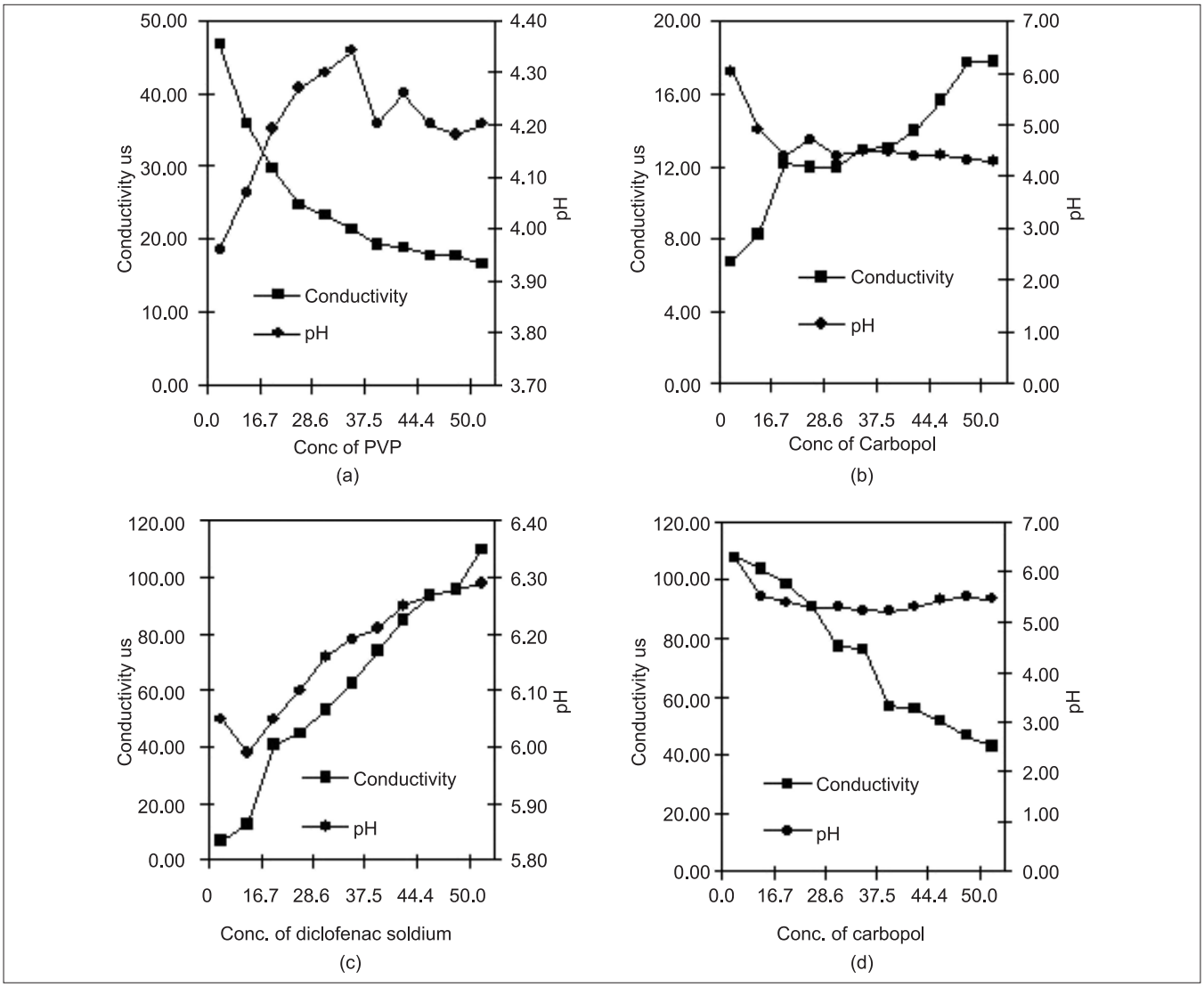

Figure 1: Conductivity and pH profiles of polyelectrolyte complexation. (a) PVP added to Carbopol, (b) Carbopol added to PVP, (c) Diclofenac sodium added to PVP and (d) Carbopol added to mixture of PVP and diclofenac sodium

Table 3: Effect of pH on the yield of CP-PVP complex

pH	% Dry polyelectrolyte complex yield (mean ± s.d.)
1.0	44.25±2.26
1.5	54.29±1.82
2.0	67.50±3.22
2.5	73.51±1.63
3.0	78.25±1.51
3.5	75.85±3.12
4.0	58.89±3.45
4.5	62.34±1.89
5.0	59.18±2.78
5.5	53.55±2.61
6.0	45.51±3.56
6.5	42.11±3.84
7.0	38.17±1.58

The complex formation between CP and PVP gradually increased up to a pH of 3.0 i.e. maximum yield obtained at this pH. Above this pH, the complex yield started decreasing. Hence, in the present study the optimum condition of pH was selected as 3.0 for CP-PVP complex formation, which is the pH of the 1% w/v solution of CP.

Effect of ionic strength on formation of polyelectrolyte complex

The effect of ionic strength on the polyelectrolyte complex between CP and PVP was investigated by adding increasing amounts of the NaCl to the complex mixture and the results are given in Table 4. Increasing the amount of NaCl was suppressed in between CP and PVP hence reduced the polyelectrolyte complex yield. It is well known that neutral salts influence the complexation process due to the screening of the charge groups on the polyelectrolytes. Increasing ionic strength resulted in decreased attraction between

Table 4: Effect of ionic strength on the yield of CP-PVP complex

Ionic strength (mM)	% Dry polyelectrolyte complex yield (mean ± s.d.)
0.0	76.35±3.24
5.0	68.49±2.18
10.0	56.53±2.59
20.0	50.42±1.23
30.0	51.84±3.29
40.0	48.33±1.98
50.0	45.15±3.12
60.0	41.22±1.74
70.0	35.68±2.86
80.0	32.17±1.58
90.0	27.65±3.44
100.0	19.25±1.62

the polyions and the tendency to form the polyelectrolyte complex.

The results of pH conductivity study indicated the formation of polyelectrolyte complexes between CP and PVP. The polymer mixing ratio, pH, and ionic strength of the polymer solutions forming the PEC influenced the complex formation. The results indicated that maximum yield of the CP-PVP complex was obtained, when PVP was added to CP at the weight ratio of 1:1 and at pH 3.0, which is the pH of 1% w/v solution of CP (2.8-3.0). Hence, in the further studies for the preparation of polyelectrolyte complexes containing diclofenac sodium 1:1 was chosen CP:PVP without adjusting the pH.

FTIR spectroscopy

The FTIR spectra [Figure 2] of polyelectrolyte complex of diclofenac sodium (DPC-60) showed all the characteristic peaks of diclofenac sodium. The sodium salt of carboxylic acid stretch (COONa) at 1580 cm^{-1}, secondary acyl amine (-NH-) stretch at 1550 cm^{-1} and chloride (Cl) stretch at 750 cm^{-1} were present in both the spectra with minor shifts. The DPC-60 spectra also showed the presence of carboxylic acid (COOH) stretch of Carbopol at 1750 cm^{-1} and amide stretch of PVP at 1720 cm^{-1}. This data clearly indicated the absence of any chemical interaction between diclofenac sodium, Carbopol, and PVP in the formation of polyelectrolyte complex. Thus, it indirectly confirmed the electrostatic interactions between the polyelectrolytes, which are responsible for the formation of these polyelectrolyte complexes.

X-ray diffraction

The X-ray diffractograms are shown in Figure 3. The spectra of diclofenac sodium showed the sharp peaks at 6.63, 8.5, 15.2 and 21.7 angle (°2 θ) indicating the crystallinity of the drug. The spectra of Carbopol and PVP did not have any sharp peaks indicating their amorphous nature. The spectra of DPC-60 showed the disappearance of the peaks at 6.63 and 8.5 and showed new peaks at 13.5, 20.5, and 24.4 angle (°2θ). This may be due to fine dispersion and entrapment of the drug in the polyelectrolyte complex.

Drug content

The drug content (mg) of the PEC microparticles was 65.20±0.56, 49.20±0.95, 46.30±0.67, and 37.6±0.96 per 100 mg of DPC-80, DPC-60, DPC-50, and DPC-40, respectively. Low standard deviation values in drug content show reproducibility from batch to batch. The drug loading efficiency of DPC-80, DPC-60, DPC-50, and DPC-40 was 81.5%, 82.0%, 92.6%, and 94.0%, respectively. The results show that there was no loss of drug during the process of complexation. The drug loading efficiency increases as the polymer concentration increases. The drug content of the prepared diclofenac sodium tablets was in the range of 98.0 to 101% (±0.6 to ±0.8). The low s.d. values indicated the uniformity in drug content for all the batches of the tablets.

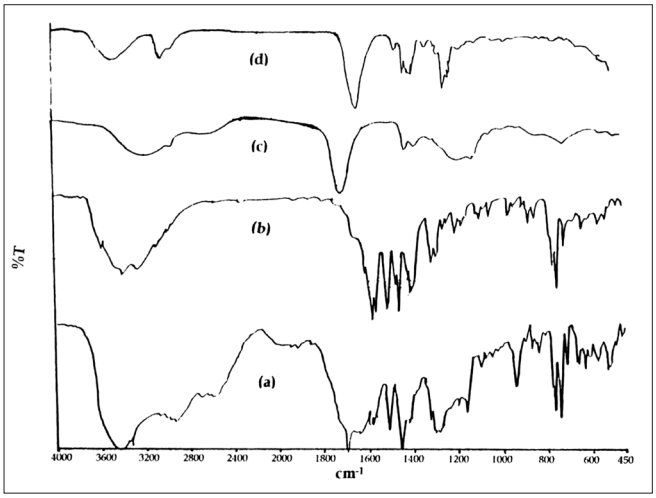

Figure 2: FTIR spectra of (a) DPC-60, (b) diclofenac sodium, (c) carbopol 934P and (d) PVP K90

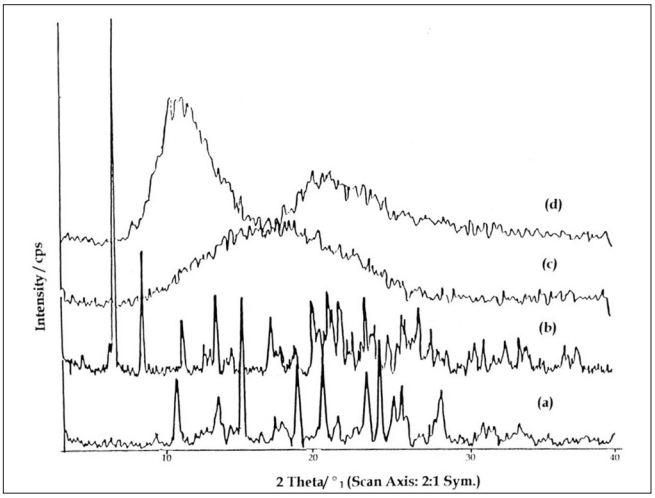

Figure 3: X-ray diffractograms of (a) DPC-60, (b) diclofenac sodium, (c) carbopol 934 P and (d) PVP K90

Dissolution studies

The results of pH, conductivity, FTIR, and XRD studies indicated that due to electrostatic interactions between the polyelectrolytes (Carbopol, PVP and diclofenac sodium), a phase separation and formation of insoluble polyelectrolyte complex occurred. The drug is dispersed in the insoluble swellable PEC particles. The drug release from these PEC micro particles was uniform and extended for longer duration of time. Within 10 min, 100% of the drug is dissolved in the case of pure diclofenac sodium, whereas the release from the PEC was extended for a period of 2 h [Figure 4]. The release of drug from the PECs decreased as the polymer concentration increased. The mechanism of drug release was established by constructing plots of cumulative percent drug released versus square root time [Higuchi diffusion[29]] and cube root of fraction of drug remained to be released versus time [erosion[30]]. The linear correlation coefficient of the slopes for the plots as shown in Figure 5 and Table 5 indicated a good correlation for the Higuchi matrix diffusion model for DPC-50 and DPC-40 and the erosion model for DPC-80 and DPC-60. The diffusion mechanism was followed for PECs with higher concentration of polymers, whereas with low concentration of polymers the erosion mechanism was followed due to faster breakdown of the PECs into smaller particles. Diclofenac sodium release from the PEC was extended for 2 h. Further studies were conducted to develop suitable tablet dosage form that can extend the duration of drug release for longer periods.

From all the prepared PECs, DPC-80 and DPC-60 were selected for the further study. These PECs possess very good flowability (angle of repose $\theta = 28$ to 29°) and compressibility (compressibility index = 15-16) and the prepared tablets showed good strength (hardness 8 to 10 kg/cm^2 and friability $<0.1\%$). The release from these two tablets DPCT 80 and DPCT 60 could extend only up to 6 h due to disintegration of tablet. To retain the shape of the tablet for longer duration an external binder (HPMC K100M) was added to the above formulations and evaluated for its drug release. The tablets DPCT80H20, DPCT60H20, and DPCT60H40 could release the drug over an extended period of time. DPCT80H20 and DPCT60H20 tablets extended the diclofenac sodium release for 8 h ($98.33 \pm 1.52\%$) and 12 h ($96.67 \pm 0.85\%$), respectively. Release of diclofenac sodium from DPCT60H40 was very slow and only $54 \pm 1.2\%$ was released in 12 h. Commercial sustained release product Voveran SR® was also evaluated for comparison, which released $94.81 \pm 0.98\%$ of the drug over a period of 12 h. When the drug release mechanism from the PEC tablets was studied for Higuchi diffusion and erodible matrix systems as shown in Figure 6 and Table 2, the linear relation of slopes indicated a positive correlation for both diffusion and erosion mechanisms of drug release. This may be due to the hydration of the tablet while dissolution causes the erosion and removal surface particles. The surface-dislodged PEC microparticles were also contributed for the drug release by the diffusion mechanism. This mechanism avoids the possibility of drug dumping due to the burst effect of matrix systems. Diclofenac sodium release form the prepared tablets showed a favorable correlation for zero-order kinetics. The commercial sustained release product showed a favorable correlation for first-order kinetics with the diffusion mechanism. Hence, the release of diclofenac sodium from the experimental tablets is by both erosion and diffusion with zero-order kinetics.

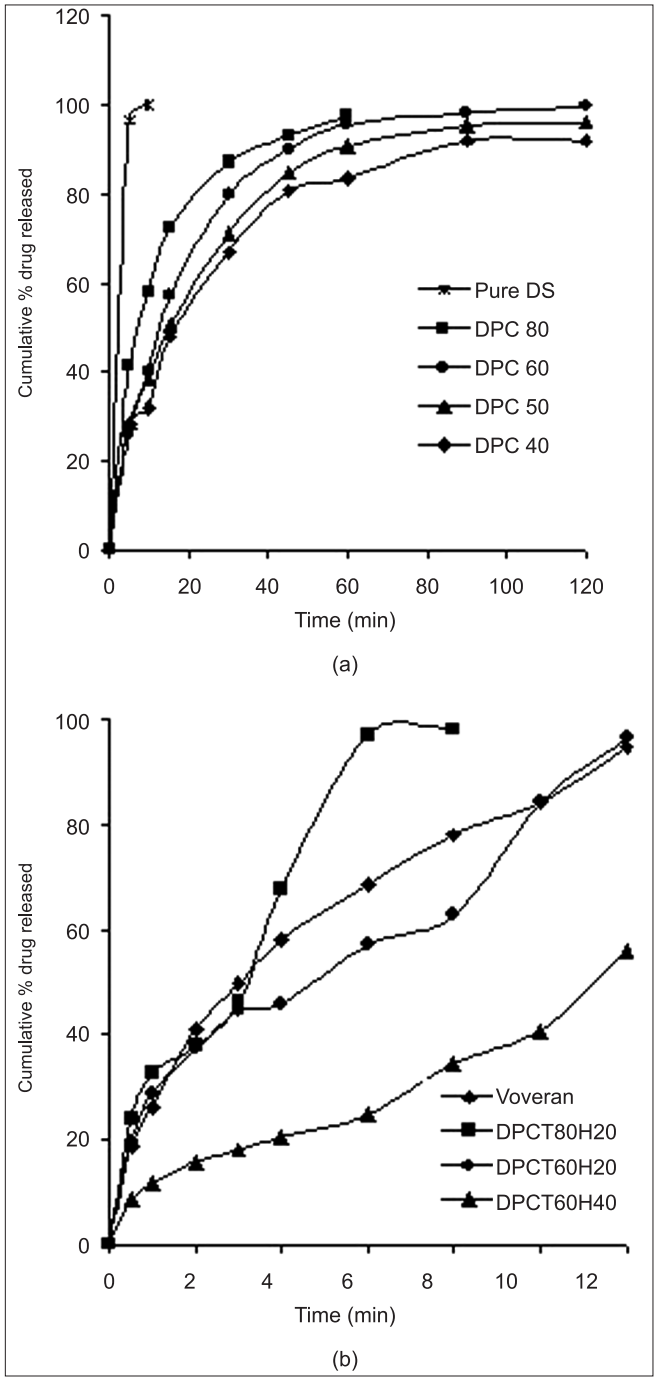

Figure 4: Comparative dissolution profiles of diclofenac sodium from (a) pure drug and PECs and (b) tablets

Statistical evaluation

The dissolution profiles of these tablets were also subjected for model independent methods proposed by Moore and

Table 5: Different release parameters of diclofenac sodium (n=3) from different formulations

Product	Zero order		First order		Diffusion	Erosion	f_1	f_2
	K_0 (mg/h^{-1})	r	K_1 (h^{-1})	r	r	r		
Pure drug	599.880	0.8804	9.6369	0.9931	-	-	-	-
DPC-80	79.098	0.8473	0.65559	0.9939	0.9642	0.9605	-	-
DPC-60	43.273	0.8255	0.51999	0.9970	0.9462	0.9569	-	-
DPC-50	42.071	0.8500	0.32134	0.9718	0.9609	0.9407	-	-
DPC-40	40.723	0.8596	0.2492	0.9630	0.9642	0.9359	-	-
Voveran SR®	6.9647	0.9505	0.03969	0.9783	0.9983	0.9900	-	-
DPCT80H20	12.0054	0.9663	0.10158	0.9500	0.9749	0.9687	18.57	43.4
DPCT60H20	6.7136	0.9676	0.04135	0.9123	0.9842	0.9576	10.29	54.83
DPCT60H40	3.9041	0.9818	0.01063	0.9685	0.9587	0.9750	55.62	23.2

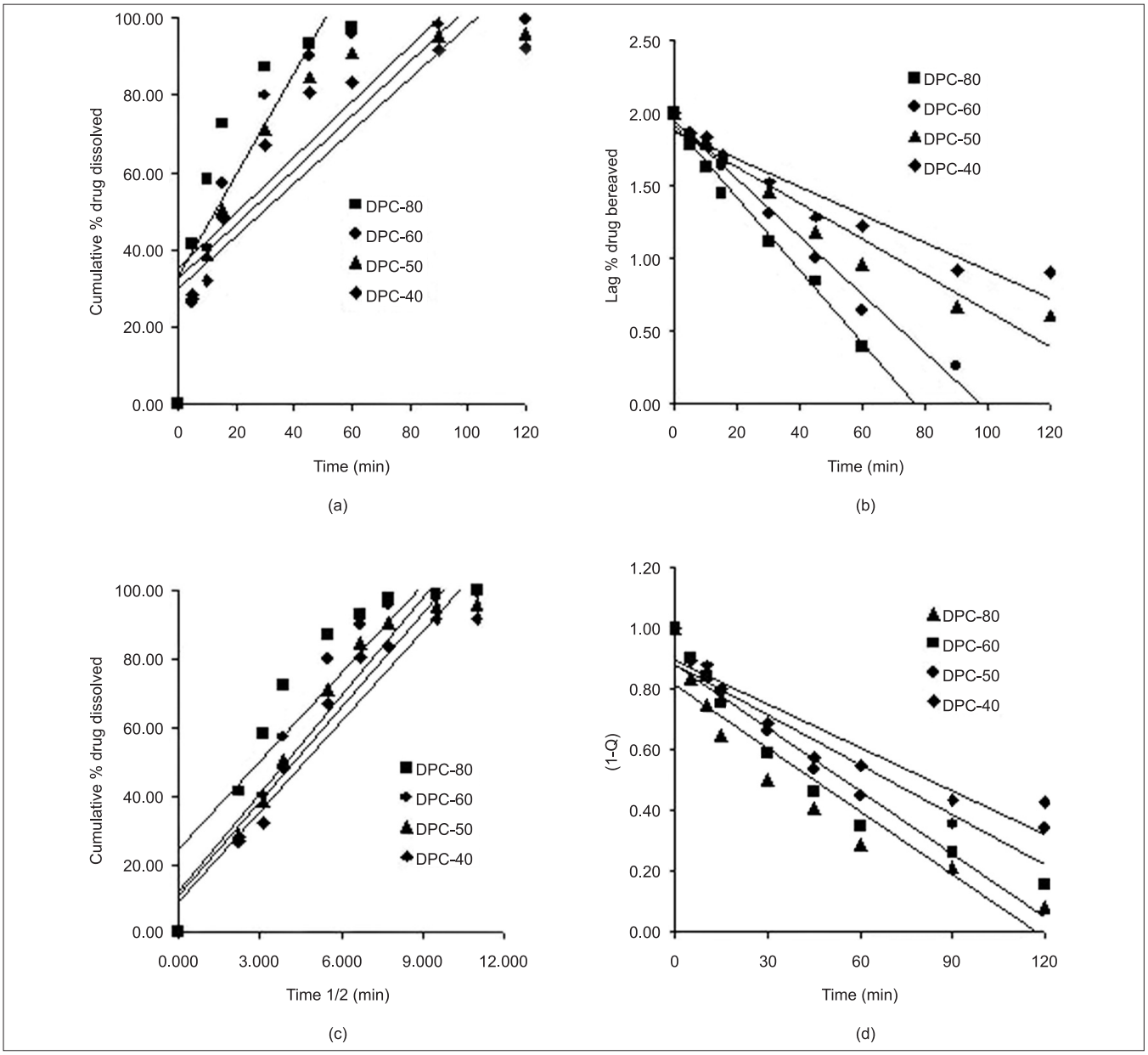

Figure 5: Linear regression plots for the dissolution profile of diclofenac sodium PECs (a) zero order plot, (b) first order plot, (c) Higuchi plot and (d) erosion plot

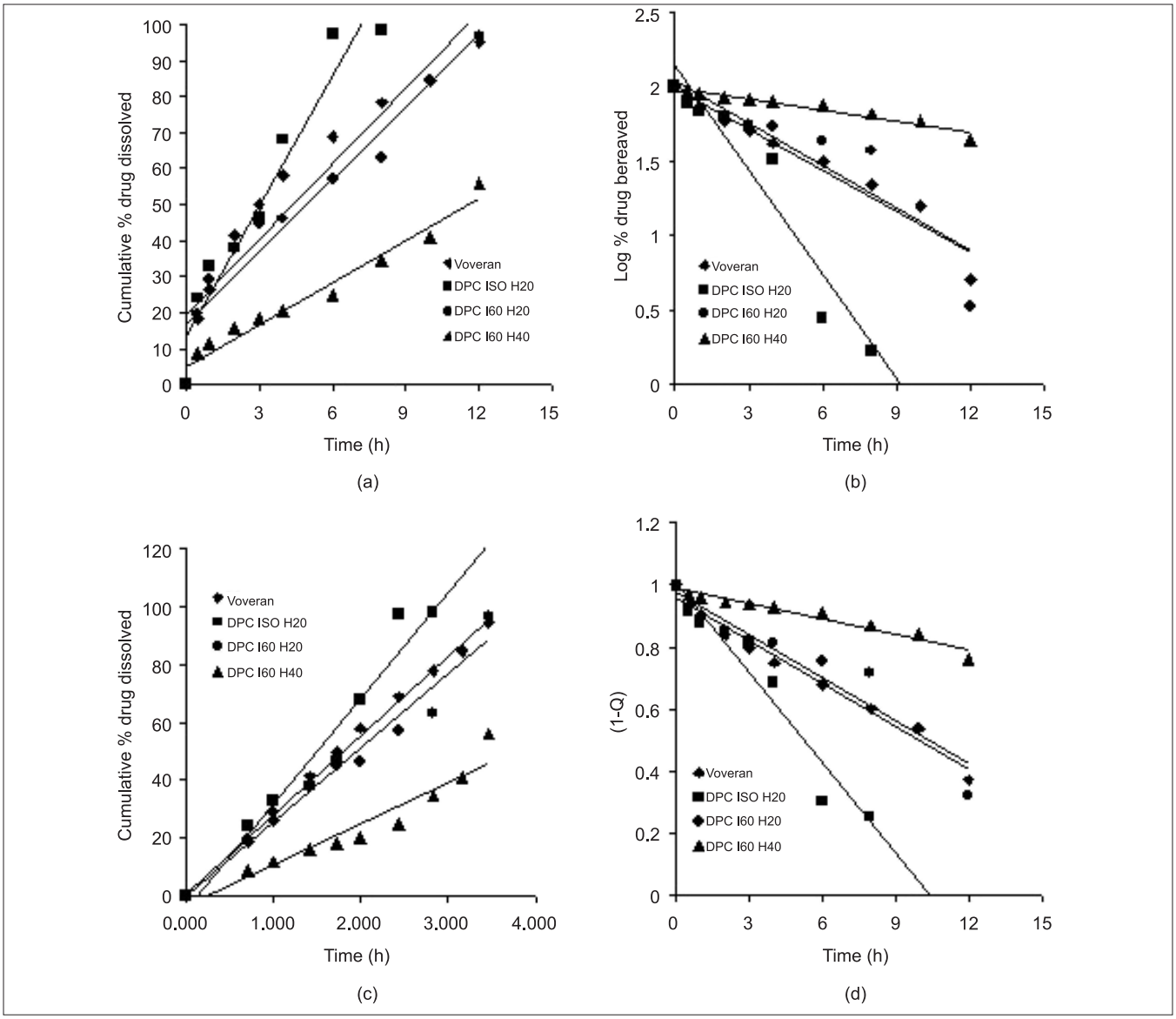

Figure 6: Linear regression plots for the dissolution profile of diclofenac sodium tablets (a) zero order plot, (b) first order plot, (c) Higuchi plot and (d) erosion plot

Flanner,[31] which involves calculation of difference factor (f_1) and similarity factors (f_2). In order to consider the similar dissolution profiles, the f_1 values should be close to 0 and values f_2 should be close to 100. In general, f_1 values lower than 15 (0-15) and f_2 values higher than 50 (50-100) show the similarity of dissolution profiles. The f_1 and f_2 values indicated a good correlation for DPCT60H20 (f_1=10.29 and f_2=54.83) when compared with commercial product. From these studies it can be concluded that DPCT60H20 was a promising formulation in controlling the release of diclofenac sodium for extended periods of time with zero-order release profile.

CONCLUSION

Polyelectrolyte complexes are the association complexes formed by the electrostatic interaction between oppositely charged particles. Polyelectrolyte complexes have gained much attention in drug delivery. In the present study it was proved that the electrostatic interactions between the polyelectrolytes (Carbopol, PVP and diclofenac sodium) are responsible for the formation of the insoluble polyelectrolyte complex. Diclofenac sodium release from these PEC micro particles was uniform and prolonged. The release of diclofenac sodium from the prepared tablets was extended for a period of 12 h and followed both diffusion and erosion mechanism with zero-order kinetics. From all the prepared diclofenac sodium tablets, DPCT60H20 gave comparable dissolution profiles with commercially sustained release tablets. The results of the study clearly indicated the usefulness of polyelectrolyte complexes in the design of oral controlled release tablets.

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