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INTERPOLYMER COMPLEXATION AND ITS EFFECT ON BIOADHESIVE STRENGTH & DISSOLUTION CHARACTERISTICS OF BUCCAL DRUG DELIVERY SYSTEMS

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ABSTRACT

During the process of development of mucoadhesive buccal delivery systems, interpolymer complex formation between carboxy vinyl polymer, which is similar to polyacrylic acid and other polymers as hydroxypropyl cellulose, carbopol-934, sodium carboxymethyl cellulose and polyvinyl pyrrolidone was studied as a function of pH. It was observed that carbopol-934 shows strong complexation with polyvinyl pyrrolidone and hydroxypropyl cellulose, but very little with sodium carboxymethyl cellulose. The degree of complexation is higher at acidic pH and decreases with an increase in pH. In further studies, when mucoadhesive buccal tablets were prepared using these polymer combinations, it was observed that the degree of complexation between the two polymers affected the rate and extent of drug release and also the bioadhesive strength of the tablets.

INTRODUCTION

Mucoadhesive dosage forms form a new type of external preparations that may render the treatment more safe and effective, not only for topical diseases but also for systemic

ones. These unique dosage forms utilize the bioadhesive property of some water soluble polymers[1]. Carbopol-934 is the most widely used polymer for formulation of mucoadhesive dosage forms, in combination with other hydrophilic polymers, to form a matrix and thereby afford controlled release property to the preparation. An interpolymer complex formation has been reported between polyacrylic acid, which is a similar compound to carbopol and other polymers such as polyoxyethylene, polyvinyl pyrrolidone hydroxypropyl cellulose etc.[2]

Hydrogen bonding between the carboxyl groups of carbopol and of polyvinyl pyrrolidone and hydroxypropyl cellulose has been reported to be the main driving force for the polyvinyl pyrrolidone/carbopol-934 and hydroxypropyl cellulose/carbopol-934 complexation[2,3]. This interpolymer complex formation was recently reported to be applicable as a device for obtaining sustained release of drugs[3]. Also, it is known to affect the release property and bioadhesive strength of the matrix tablets.

The purpose of the present study was to investigate the quantitative relationship between the complex formation among different sets of polymers and the drug dissolution behaviour from the polymer matrix, along with the respective bioadhesive strength of the matrix tablet.

PROCEDURES

Interpolymer Complexation Study

Polymers used

i) Carbopol-934

ii) Hydroxypropyl cellulose (M)

iii) Polyvinyl pyrrolidone (K-30)

iv) Sodium carboxymethyl cellulose

Method

It has been reprted that the polymer complex shows a turbidity at 600 nm where no absorption due to polymers in the solution is seen. This principle of turbidity measurement was utilised in this study.

0.02% solutions (20mg/100ml) of carbopol-934, hydroxypropyl cellulose, polyvinyl pyrrolidone, Sodium carboxymethyl cellulose were prepared in solutions of different pH (1.7 to 6.6). These were then scanned for absorption in the range of 700 to 220 nm. No absorption were seen with either of the solutions.

Three sets of the polymers were studied for complexation as under :

Hydroxypropyl cellulose/Carbopol-934

Polyvinyl pyrrolidone/Carbopol-934

Sodium carboxymethyl cellulose/Carbopol-934

For each set 0.02% solutions of the two polymers were mixed in different ratios keeping the total polymer concentration at 0.01% in all the samples. These samples were kept at $37^{O}C$ for one hour and then observed for turbidity at 600 nm.

For all the three sets of polymers, complexation study were conducted in different buffer solutions (pH 1.75, 2.47,3.18, 4.32,5.36 and 6.6) using the above method. Each study was conducted three times.

Formulation of Mucoadhesive Buccal Tablets

Model Drug : Verapamil Hydrochloride.

Polymer Combinations Studied : Hydroxypropyl cellulose (M)/Carbopol-934, Polyvinyl pyrrolidone (K-30)/Carbopol-934, Sodium carboxymethyl cellulose/Carbopol-934.

Method

The tablets were made[4] by direct compression of a physical mixture of Verapamil hydrochloride, the polymers and other

TABLE 1 : Working Formulae

Using carbopol-934 and hydroxy propyl cellulose (M) mixture

S.No.	Ingredients	Formula Code (%w/w)				
		H-1	H-2	H-3	H-4	H-5
1.	Verapamil.HCl	15	15	15	15	15
2.	HPC(M)	17	34	42.5	51	68
3.	CP-934	68	51	42.5	34	17

Compression force : 200 kg/cm^2.

Compression time : 30 seconds.

additives, on a hydraulic press used for infra-red pellet compression. The ingredients were weighed accurately and mixed by trituration in a pestle mortar. These were then passed through sieve no. 200 and compressed directly using die and punches specially fabricated for this purpose. The force of compression and compression time for each formulation have been specified along with the formulae (Table 1,Table 2 and Table 3). The tablets prepared were 13 mm in diameter and 2 mm in thickness, having an average weight of 150 mg.

All the tablets were tested for dissolution rate and bioadhesive strength. The dissolution rate was determined using the apparatus designed by Collin and Deasy[5], with some necessary modifications. Bioadhesive strength was determined on a speciallay fabricated apparatus[6], using Hamster cheek pouch as the model membrane.

RESULTS

The observations for interpolymer complexation are presented in Figure 1,2 and 3, which shows the turbidity as a function of

TABLE 2 : Working Formulae

Using carbopol-934 and polyvinyl pyrrolidone (K-30) mixture

S.No.	Ingredients	Formula Code (%w/w)				
		P-1	P-2	P-3	P-4	P-5
1.	Verapamil.HCl	15	15	15	15	15
2.	PVP(K-30)	17	34	42.5	51	68
3.	CP-934	68	51	42.5	34	17

Compression force : 200 kg/cm^2.

Compression time : 30 seconds.

TABLE 3 : Working Formulae

Using carbopol-934 and sodium carboxymethyl cellulose mixture

S.No.	Ingredients	Formula Code (%w/w)				
		S-1	S-2	S-3	S-4	S-5
1.	Verapamil.HCl	15	15	15	15	15
2.	SCMC	17	34	42.5	51	68
3.	CP-934	68	51	42.5	34	17

Compression force : 200 kg/cm^2.

Compression time : 30 seconds.

weight ratio of hydroxypropyl cellulose/carbopol-934, polyvinyl pyrrolidone/carbopol-934 and sodium carboxymethyl cellulose/carbopol-934 respectively in different pH buffers, thus confirming interpolymer complex formation. It is seen that hydroxypropyl cellulose/carbopol-934 show a maximum turbidity at weight ratio of 3:2 and polyvinyl pyrrolidone/carbopol-934 at a

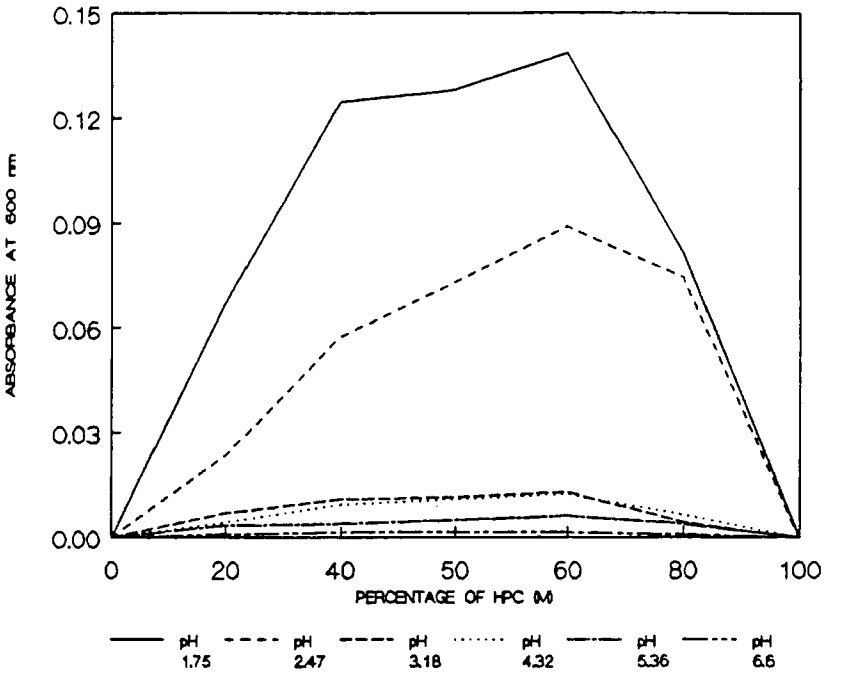

FIGURE 1
Interpolymer Complexation Study
Hydroxy propyl cellulose (M)/Carbopol-934

weight ratio of 1:1. Very little complexation is seen in case of sodium carboxymethyl cellulose/carbopol-934. It is also seen that complexation is more in the acidic range and decreases with an increase in pH.

In formulation development, the polymer combination of Sodium carboxymethyl cellulose/Carbopol-934 was dropped in earlier stages due to the lack of physical integrity for 4 hours in the tablets. The formulations P-4 and P-5 could not be studied for dissolution rate because of poor physical strength so as to stand for desired period of 4 hours. This could be due to lower concentrations of Carbopol-934 in these formulations. The dissolution curves and the bioadhesive strength of hydroxypropyl

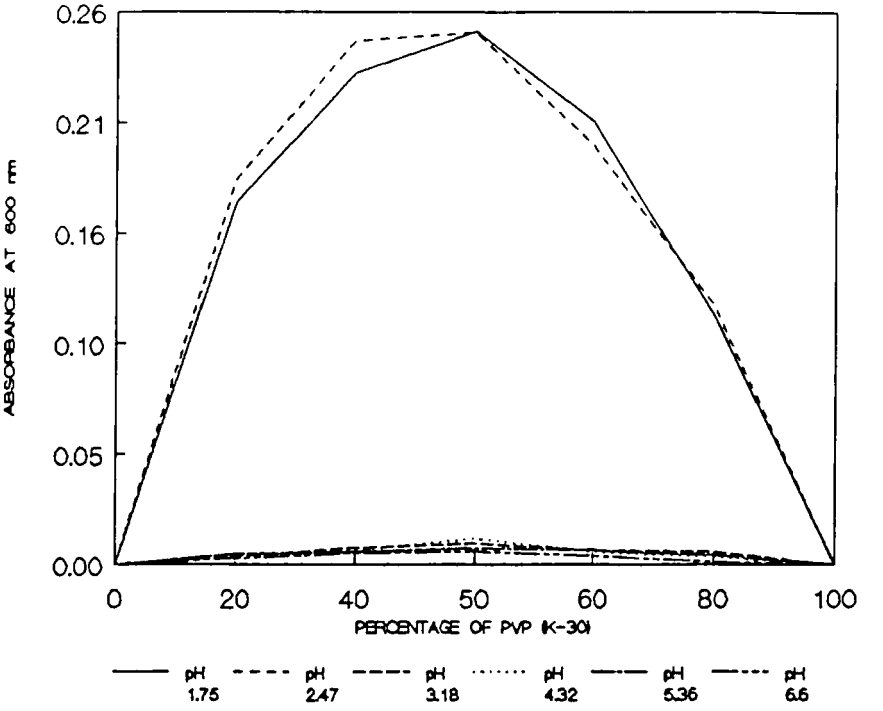

FIGURE 2
Interpolymer Complexation Study
Polyvinyl pyrrolidone (K-30)/Carbopol-934

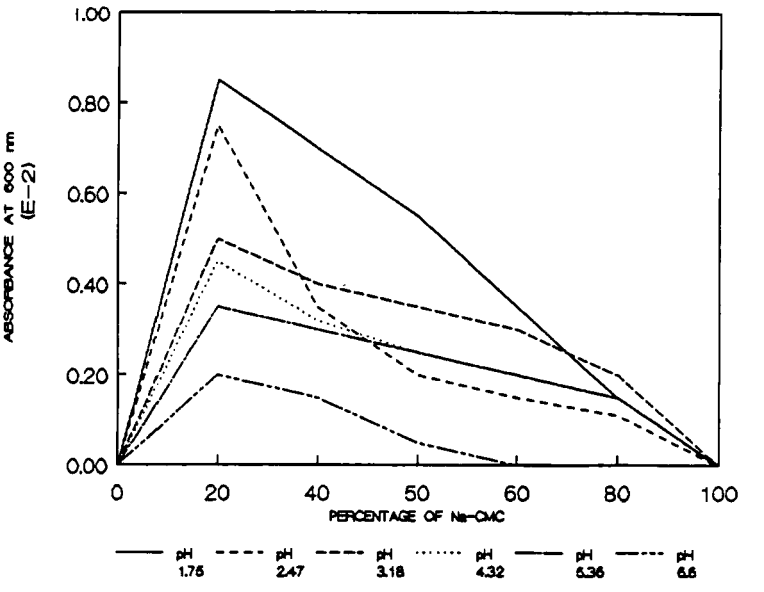

FIGURE 3
Interpolymer Complexation Study
Sodium carboxy methyl cellulose/Carbopol-934

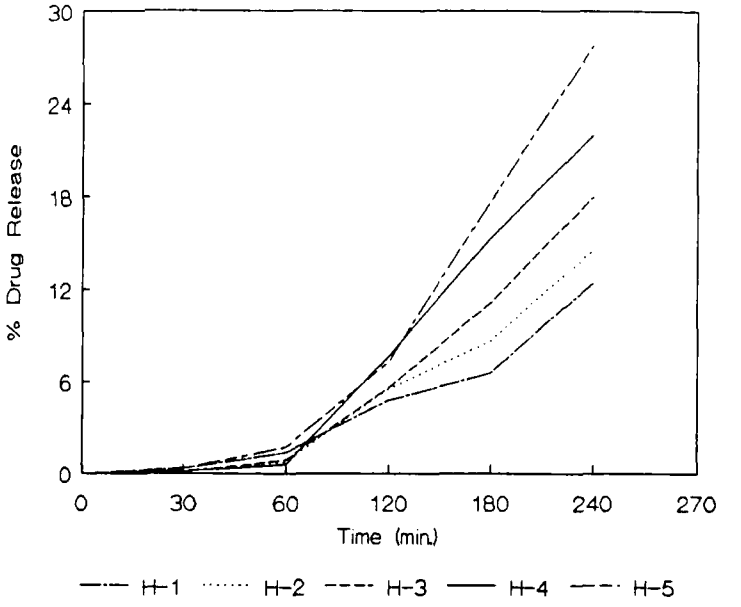

FIGURE 4
The Dissolution Curves
Hydroxy propyl cellulose (M)/Carbopol-934

cellulose (M)/carbopol-934 and polyvinyl pyrrolidone (K-30)/Carbopol-934 are shown in figure 4,5 and 6,7 respectively.

DISCUSSION

Since an interpolymer complexation has been reported[7,8] between polyacrylic acid and other polymers, an **interpolymer complexation study** was performed so as to resolve the issue of effect of this complexation on bioadhesion and drug release properties of the polymer combinations. It was observed that hydroxy propyl cellulose/carbopol-934 shows maximum complexation at a weight ratio of 3:2 and polyvinyl pyrrolidone/carbopol-934 at a weight ratio of 1:1. Sodium carboxy methyl cellulose/carbopol-934 showed negligble complexation, maximum being at a weight ratio of 1:4. It was also observed that complexation was more at acidic pH range. Maximum complexation was observed at a pH of 1.75 in all

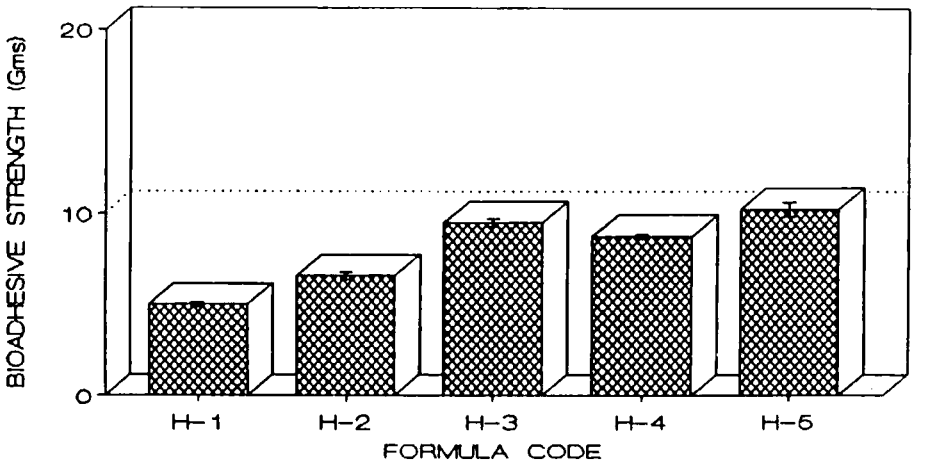

FIGURE 5
Bioadhesive Strength
Hydroxy propyl cellulose (M)/Carbopol-934

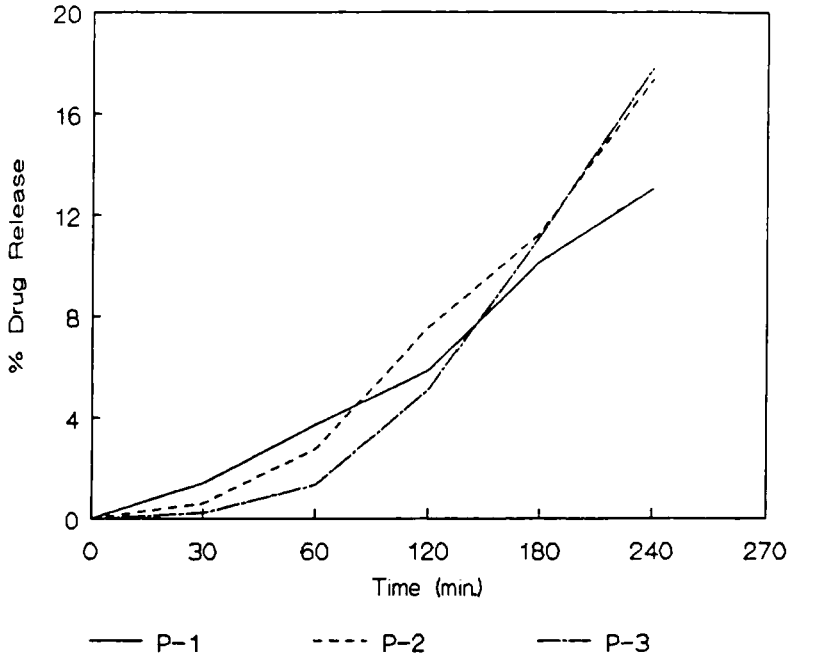

FIGURE 6
The Dissolution Curves
Polyvinyl pyrrolidone (K-30)/Carbopol-934

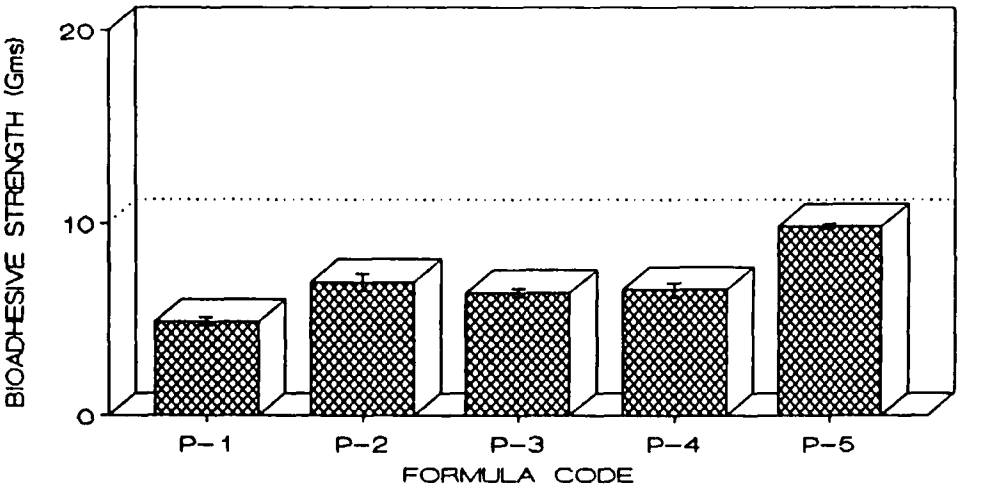

FIGURE 7
Bioadhesive Strength
Polyvinyl pyrrolidone (K-30)/Carbopol-934

tne three cases. The complexation was seen to decrease with an increase in pH and above pH 4.5, complexation was negligible. The effect of this complexation on dissolution and bioadhesion of the formulations developed was observed in later studies.

The **Dissolution study** of tablets consisting of hydroxypropyl cellulose/carbopol-934 and polyvinyl pyrrolidone/carbopol-934 revealed that drug release increases with an increase in the percentage of hydroxypropyl cellulose and polyvinyl pyrrolidone, the water soluble polymers. Also, in both the cases, a lag time exists concerning drug release. Before 1 hour, the drug is released at a very slow rate followed by an increased release rate, almost linear with time in later stages. Maximum lag time is observed with formulations H-4 and P-3, which contain the polymers in a combination ratio showing maximum complexation, thus indicating the formation of strongest matrix .

The reason for this **lag time** may be the fact that a three dimentional network like structure is formed by complex formation

following the penetration of dissolution medium into the tablet. Though the pH value of the dissolution medium, isotonic phosphate buffer (pH 6.6) was higher than the critical pH for complexation, the pH value inside the polymer matrix could be low enough for the complexation owing to the acidity of carbopol-934, independent of the pH value of the dissolution medium in the initial dissolution stage. As a result it could be inferred that the drug was tightly held in the matrix initially and with the continuous penetration of the dissolution medium, the pH value in the matrix increased gradually. When it reached the pH value critical for decomplexation, the network structure disappeared and the drug was released rapidly.

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