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Preparation and Evaluation of Mucoadhesive Microspheres of Atenolol and Propranolol

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Abstract : Mucoadhesive microspheres were prepared by an interpolymer complexation poly(acrylic acid) (PAA) with poly(vinyl pyrrolidone) (PVP) to increase gastric residence time and a solvent diffusion method. The complexation between poly(acrylic acid) and poly(vinyl pyrrolidone) as a result of hydrogen bonding was confirmed by the shift in the carbonyl absorption bands of poly(acrylic acid) using FT-IR. A mixture of ethanol/water was used as the internal phase, corn oil was used as the external phase of emulsion, and span 80 was used as the surfactant. Spherical microspheres were prepared. The particle size increased as the content of water was increased. The mean particle size increased with the increase in polymer concentration. The adhesive force of microspheres was equivalent to that of Carbopol. The release rate of atenolol from the complex microspheres was slower than the PVP microspheres at pH 2.0 and 6.8.
Keywords Mucoadhesive, microsphere, Gastric residence time, Complexation.

1. Introduction

Oral controlled release systems continue to be the most popular ones among all the drug delivery systems as it offers several advantages over the conventional systems like:

1. Improve patient's compliance and convenience due to less frequent dosing of drug.
2. Reduction in fluctuation of steady state plasma level and therefore helps in better control of disease condition.
3. Maximum utilization of drug enabling reduction in total amount of dose administered.
4. Reduction in health care cost through improved therapy, shorter treatment period and less frequency of dosing.[1, 2]

The problem frequently encountered with controlled release dosage forms is the inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine, due to the rapid gastrointestinal transit phenomenon of the stomach which may consequently diminish the extent of absorption of many drugs since almost most of the drug entities are mostly absorbed from the upper part of the intestine, therefore it would be beneficial to develop a sustained release formulation which remain at the absorption site for an extended period of time. Several approaches have been immersed to prolong the residence time of the dosage forms at the absorption site and one of these is the development of oral controlled release bioadhesive system. Various gastrointestinal mucoadhesive dosage forms, such as discs, microspheres, and bilayered tablets, have been thoroughly prepared and reported by several research groups.[3]

The Preferably used mucoadhesive materials include chitosan, hydroxypropyl cellulose, poly(acrylic acid)(PAA) and their derivatives. Although, PAA is considered to be one of the best mucoadhesive polymers,the high water solubility of PAA critically limits itsuse as a carrier for the sustained release of a drug. PAA based interpolymer complexation has been examined in order to reduce the water solubility of PAA. Inthose studies, it was shown that the water solubility of PAA could be reduced and the adhesive force could be maintained via the complexation of the PAA with proton accepting polymers such as poly(ethyleneglycol), poly(ethylene glycol) macromer, poloxamer and poly(vinyl pyrrolidone) (PVP). It was also observed that PAA and PVP aggregate and precipitate in ethanol and water in a relatively short period of time, resulting in the formation of a PVP/PAA interpolymer complex, suggesting that the intensity of hydrogen bonding between PAA and PVP is quite strong. It was believed that this strong complexation could be utilized to prepare mucoadhesive microspheres. Each component is soluble in water. However, when they come together they form a complex and precipitate. If a PAA solution and PVP solution can be emulsified and droplets of each emulsion

collides afterwards, complexation should occur, which will solidify to form microspheres[4,5,6].

2. Materials and methods

2.1. Materials

The PVP (MW: 42,500) was obtained from BASF(Ludwigshafen). The PAA (MW: 450,000) was purchased from Aldrich (Milwaukee). Sorbitan monooleate (span 80) was purchased from Junsei Chemical (Tokyo). Corn oil was acquired from CJ Corporation (Seoul). All other chemicals were of reagent grade available commercially.

2.2. Methods

2.2.1. Preparation of mucoadhesive microspheres

The mucoadhesive microspheres were prepared by interpolymer complexation and solvent diffusion method. PAA (0.2 g) was dissolved in 4.8 g of ethanol/water (7/3, w/w) mixture and PVP (0.32 g)was dissolved in 1 g of ethanol/water (7/3, w/w) mixture unless otherwise specified. When two solutions were combined together, the concentration of polymer, PAA and PVP, was 8.2%. Using a syringe, the PAA solution and PVP solution were sequentially dropped into200 ml of corn oil, which was used as the external phase. The external phase contained 0.04% v/v of span80 (sorbitan monooleate) as a surfactant. They were stirred with a magnetic bar at 500 rpm at an ambient temperature over 36 h. The microspheres were gradually hardened and the hardened microspheres were collected by filtration. They were washed several times with *n*-hexane and dried at 80 ◦C over 12 h. The yield was calculated by dividing the weight of the collected microspheres by the total weight of all the non-volatile components used for preparing the microspheres. In order to examine the effect of the amount of internal phase used, the effect of the solvent ratio of the internal phase, the surfactant concentration, and the polymer concentration on the formation of microspheres, each relevant variable was changed with other variables fixed as previously described. The effect of the stirring speed on the formation of the microspheres was investigated using stirring speeds of 300, 400 and 500 rpm. In order to prepare acetaminophen-loaded microspheres, atenolol was dissolved in PAA solution and PVP solution, respectively. The concentration of acetaminophen in each polymer solution was 5% of the polymer used. In order to prepare PVP microspheres, PVP (8.2%)and drug (5%) were dissolved in ethanol/water mixture (7/3, w/w). PVP microspheres were prepared in the same way as described previously and bservation seen as in table.1

2.2.2. IR spectroscopy

The infrared absorption spectra of the PAA, PVP,and PAA/PVP complex microspheres were obtained using a FT-IR spectrophotometer (FT-IR 401, Jasco). The samples were pressed into a pellet before measuring their infrared absorption spectra. To prepare the pellets, a few milligrams of the sample were ground together in a mortar with about 100 times the quantity of KBr[7,8]. The finely ground powder was introduced into a stainless steel die. The powder was then pressed in the die between polished stainless steel anvils at a pressure of about 10 t/in.2.

2.2.3. Particle size analysis

The mean particle size of the microspheres was measured using a particle size analyzer (HELOS/BF, Sympatec GmbH).

2.2.4. Measurement of adhesive force

A motor driven auto peeling tester was used to measure the adhesive force of the PVP/PAA interpolymer microspheres and Carbopol 971 to a plastic (polypropylene) plate. The microspheres were pressed into a tablet before measuring adhesive force. The specimens, discs with the area of 1.33 cm2, were wetted with pH 2.0 HCl solution at room temperature for 15 s before testing, and then placed between two plastic plates. The plates subjected to a pressure of 1.2 N/cm2 for 60 s before measurements were made. The peak force required to detach the disc from the plastic plate was measured.

2.2.5. Morphology

The morphology of the microspheres was examined by field emission scanning electron microscopy (S-4700, Hitachi). The sample was mounted on to an aluminum stub and sputter-coated for 120 s with platinum particles in an argon atmosphere[9,10,11].

2.2.6. Release of atenolol from the microspheres

The drug release test was carried out using a dissolution tester (DST 810). The PAA/PVP complex or PVP microspheres loaded with Atenolol 50 mg was placed in 500 ml of a release medium and stirred at 100 rpm at 37 ◦C. The release media tested were pH 2.0 HCl solution and pH6.8 phosphate buffer solution. An aliquot of the release medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The collected samples were filtered through a 0.45 _m-syringe filter, and analyzed by HPLC(Shimadzu Scientific Instruments), consisting of a UV detector (SPD-10A), a pump(LC-10AD), and an automatic injector (SIL-10A), in order to determine the amount of Atenolol released from the microspheres. The wavelength of the UV detector was 254 nm and a reversed-phase column (Luna 5_m C8, Phenomenox) was used[12,13,14]. The column temperature was maintained at 30 ◦C. The flow rate was 1 ml/min, and the mobile phase was acetonitrile/water (30/70).

3. Results and discussion

3.1. Preparation of PAA/PVP complex microspheres

PAA and PVP are known to form a complex in an aqueous solution and in some organic solvents such asethanol. Once they form a complex, the aqueous solubility greatly decreases without losing the

mucoadhesive properties of PAA and the complex formed precipitates in the solution. This principle was utilized to prepare the mucoadhesive microspheres. The PAA solution and the PVP solution were sequentially dropped and dispersed in corn oil. Corn oil was chosen as the external phase because the ethanol/water mixture as an internal phase is not miscible with corn oil and the complex is not soluble in it. As the dispersed droplets of the PAA solution collided with those of the PVP solution in corn oil, they formed an inter polymer complex. The droplets of the PAA/PVP complex gradually solidified and hardened as the ethanol and water diffused out of the internal phase. The complexation between the PAA and PVP via hydrogen bonding was confirmed by a shift in the carbonyl absorption bands of PAA using FT-IR. The PAA alone has a band at 1716.3 cm−1 due to intra molecular hydrogen bonding of the carboxyl group of PAA. However, some of the intra molecular hydrogen bonding breaks when PAA and PVP forms an inter polymer complex, since new hydrogen bonds are formed between the carboxyl groups of PAA and the carbonyl groups of PVP. Therefore, once an inter polymer complex has formed, the carbonyl absorption band of PAA shifts to a higher wave number. The FT-IR spectrum of the prepared microspheres showed that the carbonyl absorption band of PAA at 1716.3 cm−1 had shifted to a higher wave number at 1735.6 cm−1 (Fig. 1). These results suggest that mucoadhesive microspheres were formed by an inter polymer complexation between PVP and PAA. In order to identify the optimum preparation conditions, the effects of the various experimental parameters, such as the internal phase volume fraction, the solvent ratio of the internal phase, the surfactant concentration, the polymer concentration, and the stirring speed, on the formation of microspheres were investigated[7,8].

3.2. Morphology

The morphology of the microspheres was examined by scanning electron microscopy. The view of the microspheres showed a spherical shape with a smooth surface morphology (Fig. 2). The inside of the microspheres was completely filled, indicating that complexation had occurred everywhere within the microspheres.

3.3.Dissolution of microspheres

Fig. 3 shows the dissolution rates of the PAA/PVP complex microsphere and PVP microsphere at pH 2.0 and 6.8 after 1, 2 and 4 h. The degree of dissolution of the PVP microsphere was 100% in 1 h at both pHs tested. However, that of the PAA/PVP complex microsphere was significantly reduced due to complex formation and did not dissolve completely after 4 h at both pHs. The dissolution rate of the complex microspheres was pH dependent, and the dissolution rate at pH 2.0was much slower than that of the complex microspheres at pH6.8. This can be explained by the dissolution characteristics of the PAA based complex. When the pH is lower than the p*K*a of PAA (4.75), the majority of the carboxyl groups of PAA are not ionized, and the hydrogen bonds between PAA and PVP in the complex can be maintained, leading to a slower dissolution rate .However, when the pH is higher than the p*K*a of PAA, the majority of carboxyl groups of PAA are ionized and the hydrogen bonds cannot be maintained, leading to a higher dissolution rate. This shows that PAA/PVP complex microspheres can the stomach.

3.4. In vitro drug release

Fig. 5 shows the in vitro release profile of a model drug, atenolol, from the microspheres made from PAA/PVP complex and PVP at pH 2.0 and 6.8.Microspheres were made using PVP only to compare the release rate. The release rate of atenolol from the PAA/PVP complex microspheres was significantly slower than the PVP microspheres at pH 2.0 and 6.8.There were no significant difference in the release rate of atenolol from the PVP microspheres at pH2.0 and 6.8. However, the release of propranolol from the PVP/PAA complex microspheres at pH 2.0 was much slower than at pH 6.8. Hydrogen bonding between PAA and PVP was so strong at a pH much lower than the p*K*a of PAA that they barely dissociated into PAA and PVP. These results suggest that the PVP/PAA microspheres can be used as a drug-delivery system for treating gastric diseases.

4. Conclusions

A mucoadhesive microsphere was prepared by a solvent evaporation and interpolymer complexation method. The dissolution rate of the complex microspheres was significantly retarded when compared with that of the PVP microspheres, particularly at pH 2.0. The results of this study indicate that it may be feasible to use PAA/PVP mucoadhesive microspheres as a gastric retentive drug delivery system for antihypertensive action. The release rate of the Beta-blockers agents will be retarded due to the slower dissolution rate of the complex polymer.

Table .1 : Comparison of the yields, loading efficiencies and particle sizes of the PAA/PVP complex microspheres (*n*=3)

Loaded drug	Yield (%)	Loading efficiency (%)	Amount loaded (mg/g)	Particle size (_m)
Non	83.1±0.7	–	–	71.3±11.8
Atenolol	87.9±1.6	58.2±4.2	27.9±1.9	63.2±4.9
Propranolol	89.9±5.1	94.1±5.3	47.4±2.8	64.8±4.3

The value are represented as mean±S.D., where S.D. is the standard deviation.

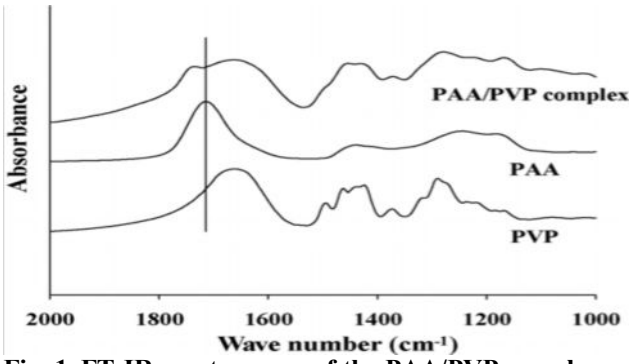

Fig. 1. FT-IR spectroscopy of the PAA/PVP complex microspheres, PAA or PVP.

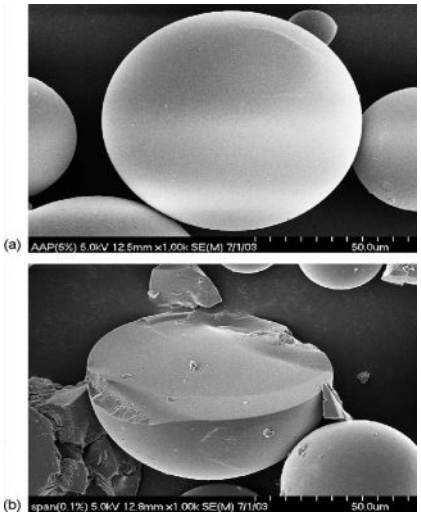

Fig 2. Morphology of the complex microsphere: the surface (a) and the inside (b) of the microsphere

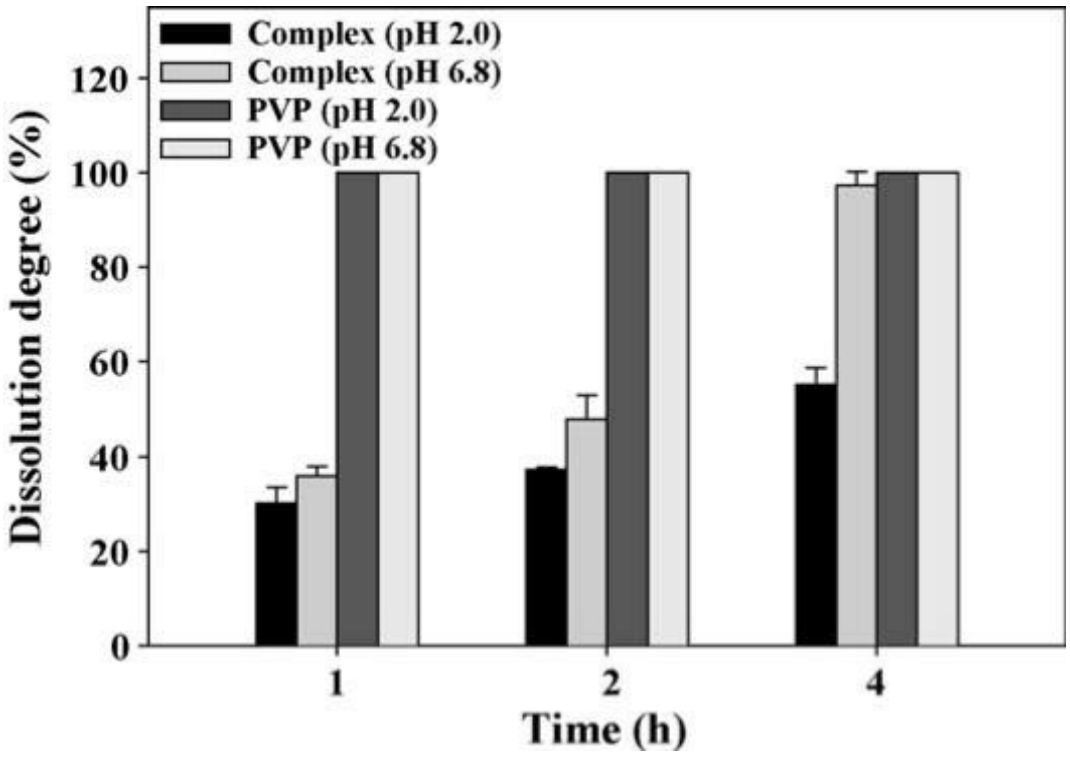

Fig. 3 Dissolution rates of the PAA/PVP complex microsphere and PVP microsphere at pH 2.0

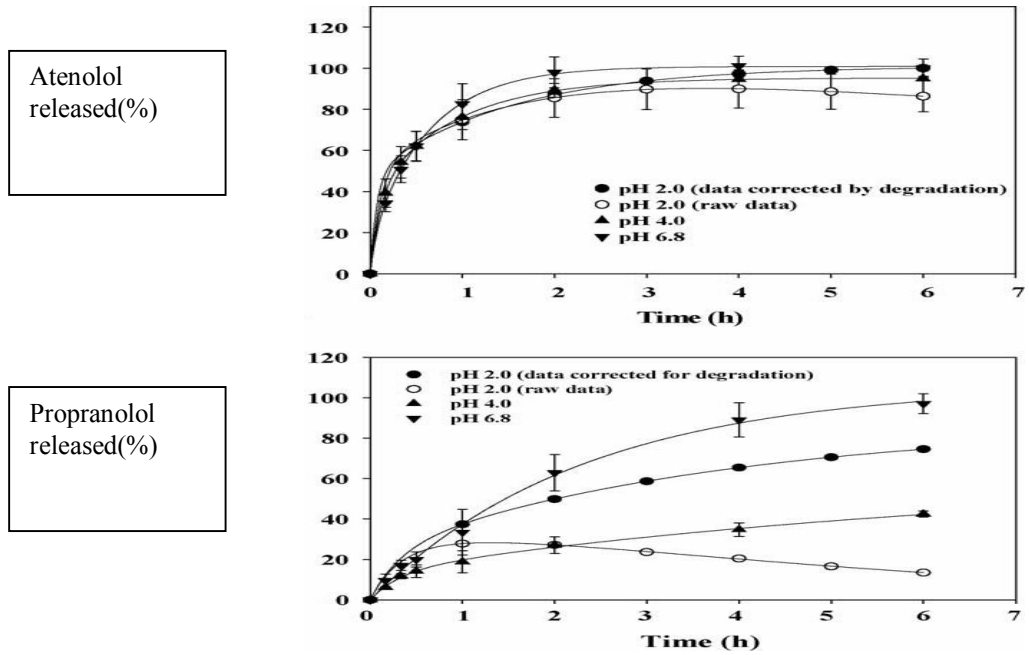

Fig. 4. In vitro release of atenolol (a) and propranolol (b) from the PAA/PVP complex and the PVP microspheres at pH 2.0, 4.0 and 6.8 at 37 .C (*n* = 3).

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