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ORIGINAL ARTICLE

Preparation and evaluation of a novel gastric mucoadhesive sustained-release acyclovir microsphere

Hongfei Liu[1], Weisan Pan[2], Peng Ke[3], Yixiang Dong[1] and Lijun Ji[1]

[1]Department of Materials, Imperial College London, London, UK, [2]Department of Pharmaceutics, Shenyang Pharmaceutical University, Shenyang, PR China and [3]Department of Pharmaceutics, School of Pharmacy, University of London, London, UK

Abstract

Objective: The objective of this study was to prepare a novel gastric mucoadhesive sustained-release acyclovir (AV)-resinate microsphere. *Methods*: First, AV absorption ratio was quantified in a rat gastrointestinal (GI) tract model. AV-resinate was prepared by bath method and used as cores to prepare microspheres by an emulsion solvent diffusion technique with carbopol 934 as coating material. GI transit test of the prepared microspheres was carried out in rats and beagle dogs, followed by the in vivo bioavailability evaluation of the microspheres in beagle dogs. *Results*: The AV absorption ratio in different segments of rat's GI track for 3 hours was as following: stomach 9.46 ± 0.62%, duodenum 20.22 ± 1.50%, jejunum 15.7 ± 1.33%, ileum 9.15 ± 1.01%, and colon 4.59 ± 0.48%. These results showed that AV was mainly absorbed in the stomach and upper intestine. The average diameter of the microspheres was 115.3 μm. The microspheres had a drug content of 33.3 ± 0.7% (w/w) and a sustained-release profile for 12 hours in vitro. The mucoadhesive test in rats and beagle dogs showed that most of the microspheres were retained in the stomach 6 hours after oral administration. The in vivo pharmacokinetics test revealed that the microsphere and reference (AV tablets) preparations have no significant difference for C_{max}. The t_{max} has increased from 2.33 hours (reference) to 5 hours (test). Meanwhile, the relative bioavailability of AV microspheres was 145%. *Conclusion*: A novel AV-resinate microsphere was prepared. The microspheres were proved to be gastric mucoadhesive and sustained-release with higher bioavailability.

Key words: *Acyclovir; carbopol; ion-exchange resin; mucoadhesive; in vivo microsphere*

Introduction

Acyclovir (AV) is a synthetic analogue of purine nucleosides with antiviral activity. It is active against type I and type II herpes simplex virus and varicella-zoster virus. It has shown high specificity against infected cells[1].

According to the type of infection, AV can be administered by intravenous infusion at a concentration not greater than 5 mg/mL, by oral administration five times a day with each dose of 200 mg or by topical administration as ointment or cream containing 5% (w/v) drug 5–6 times daily[2]. Long-term administration of AV (6 months or longer) is required in immunocompetent patients with relapsing herpes simplex infections.

The oral administration route has several shortcomings. Because of AV's poor solubility, when orally administered, AV is poorly absorbed from the gastrointestinal (GI) tract. The bioavailability is only 13–20%[3]. In certain type of infection, the single oral dose could be as high as 800 mg, which is inconvenient for the patient to take. Additionally, AV has a short plasma half-life of 3 hours, which requires administration 5–6 times daily[3].

Recently, several studies had been carried out to increase the bioavailabilty or decrease the side-effect of the AV on the intravitreal, nasal, vaginal, and ocular drug deliveries[4–8]. However, few studies have been made to overcome all the above-mentioned shortcomings together. In this study, a novel gastric mucoadhesive AV-resinate microsphere was prepared for oral administration with sustained drug release, improved bioavailability, and easy to administer tailored doses specific for individual cases.

Address for correspondence: Dr. Hongfei Liu, Department of Materials, Imperial College London, Exhibition Road, London SW7 2AZ, UK.
E-mail: liuhongfei2000@163.com

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Ion-exchange resins are high-molecular-weight polyelectrolytes, which can exchange mobile ions of similar charge with the surrounding medium. Recently, they have been applied to drug delivery systems[9–12], primarily controlled release systems in the liquid form and taste masking. The sustained-release microspheres using ion-exchange resin as the drug carrier have been proved successful for the sustained-release liquid drug delivery[13]. However, few investigations have been made on the application of the ion-exchange resins in mucoadhesive dosage form. In this study, ion-exchange resin was applied in the mucoadhesive drug delivery.

Carbopol polymers are poly(acrylic acid) cross-linked with polyalkenyl ethers or divinyl glycol, which can be used to form highly viscous gels. Since the 1950s, carbopol polymers have been widely applied in the pharmaceutical areas, such as thickening agent, suspending agent, gel base, bioadhesion material, and matrix materials in the controlled release preparation[14,15].

The purpose of this study was to prepare gastric mucoadhesive sustained-release AV-resinate microspheres. AV absorption test was carried out in rat's GI tract; AV-resinate was prepared by the bath method and then used as core to prepare microspheres using the emulsion solvent diffusion technique with carbopol 934 as coating material. The drug content, particle size, and in vitro drug release were investigated. The mucoadhesive test of the prepared microspheres was investigated in rats and beagle dogs. Finally, the in vivo evaluation for the gastric mucoadhesive sustained-release AV-drug resinate microspheres was carried out in beagle dogs.

Materials and methods

Materials

AV and ganciclovir were obtained from the Sigma-Aldrich Corporation (St. Louis, MO, USA). The cation-exchange resins Amberlite® IRP69 (sodium polystyrene sulfonate) were a gift from Rohm and Haas Company, Philadelphia, PA, USA. Carbopol 934 was a gift from Noveon Company (Cleveland, OH, USA). Liquid paraffin, polyethylene glycol (PEG) 400, and span 80 were obtained from the Sigma-Aldrich Corporation.

GI absorption in situ

Male Wistar rats weighing 250 ± 20 g for GI absorption experiments were supplied by the Center of Experimental Animals, Shenyang Pharmaceutical University, Shenyang, China. All studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication No. 85–23, revised in 1985) and were approved by the Department of Laboratory Animal Research at Shenyang Pharmaceutical University. Animals were acclimatized for at least 5 days before the experiments and housed in cage (6 each) with free access to food and drinking water. The perfusion solution was Krebs–Rings buffer solution containing 7.8 g NaCl, 0.35 g KCl, 1.37 g $NaHCO_3$, 0.02 g $MgCl_2$, 0.22 g NaH_2PO_4, and 1.48 g glucose in 1000 mL purified water.

Absorption study of AV in rat stomach

The tests were performed as previously described[16]. Briefly, six male Wistar rats were placed in individual cage and fasted overnight before the experiment with free access to water. The treatment of rats was as follows: each of them was anesthetized with an intraperitoneal injection of 1% sodium pentobarbital (0.4 mL/100 g bodyweight). Upon verification of the loss of pain reflex, the abdomen was opened with a midline longitudinal incision about 3 cm long. The pylorus of the stomach was cannulated with glass tubing. A small incision was then made in the cardia. After rinsing the stomach with artificial gastric juice, the cardia was ligated and 4 mL artificial gastric juice containing 10 μg/mL AV was injected into the stomach. The pylorus was then ligated and the stomach was put back into the abdomen for 3 hours. At the end of the experiment, the perfusate solution in the stomach was extracted and filtered. The AV concentration in the filtrate was determined by methods described below and AV absorption percentage was calculated as follows:

$$A = \frac{W_0 - W_3}{W_0},$$

where A is the absorption percentage of AV in rat's stomach (%), W_0 is the AV quantity in stomach before the absorption test, and W_3 is the AV quantity in stomach after the absorption test.

Absorption study of AV in different intestinal segments of rats

The study followed the method described by Michel et al.[17] Six male Wistar rats were fasted overnight before experiment with free access to water. The predisposal treatment of rats was described in absorption study of AV in rat stomach. Then 10-cm-long segments of duodenum (1–11 cm distal to pyloric sphincter), jejunum (15–25 cm distal to pyloric sphincter), ileum (20–30 cm proximal to cecum), and colon (2–12 cm distal to cecum) were cannulated and ligated with both ends. The selected intestinal segments were gently washed with prewarmed normal saline (37 ± 1°C) and attached to a peristaltic pump (BT00-100M, Shanghai Longer Precision Pump Co. Ltd., Shanghai, China). One

hundred milliliters of 10 μg/mL AV perfusion solution was perfused at a flow rate of 1.5 mL/min for 3 hours for each segment. At the end of the experiment, the remaining perfusate solution was filtered and the AV content was quantified by methods described below. The AV absorption percentage was calculated as follows:

$$B = \frac{K_0 - K_3}{K_0},$$

where B is the absorption percentage of AV in different intestinal segments of rats (%), K_0 is the AV quantity in different intestinal segments of rats before the absorption test, and K_3 is the AV quantity in different intestinal segments of rats after the absorption test.

Analysis of AV in absorption study

The AV amount in absorption study sample was determined using a high-performance liquid chromatography (HPLC) system that was equipped with an LC-10AT HPLC pump (Shimadzu, Kyoto, Japan), a SPD-10AVP UV Spectrometer detector (Shimadzu), and a Diamonsil C_{18} column (200 × 4.6 mm, 5 μm particle size; Dikma, Beijing, China). The sample injection volume was 20 μL and the UV detection wavelength was 252 nm. Analysis was performed at 30°C using a mobile phase (methanol and water, 10:90, v:v) at a flow rate of 1.0 mL/min.

Analysis methods were validated according to the established international guidelines and requirements (Validation of analytical Methods: Definitions and Terminology, ICH Topic Q2A, and Validation of Analytical Procedure: Methodology, ICH Topic Q2B). No interfering peaks were detected at the retention times of AV (6.8 minutes). A linear correlation ($r > 0.999$) was obtained between the peak area and AV concentration at the range of 1–10 μg/mL. Recovery and accuracy of the method were evaluated at concentrations of 10, 5, and 1 μg/mL. The recovery was 99.3 ± 0.6%, 98.5 ± 0.7%, and 98.9 ± 0.7%, respectively. The bias% of the intra- and interday accuracy was 0.56–0.77% and 0.71–0.92%.

Determination of AV solubility in different medium

Excessive AV was added to water under magnetic stirring, 0.005, 0.01, 0.025, and 0.05 mol/L HCl until saturated at 25°C. The solution was then filtered and the drug dissolved was measured by UV spectrophotometry at a wavelength of 252 nm.

Preparation of AV-resinates microspheres

The AV-resinates were prepared by the bath method[18]. Twenty grams ion-exchange resins were suspended in 2000 mL HCl solution (0.01 mol/L) containing 10 mg/mL AV under magnetic stirring at 30°C for 4 hours. The AV-resinates were then washed with deionized water and dried at 40–60°C.

The AV-loaded resins were then re-suspended in 20% (w/v) PEG4000 water solution. After stirring for 0.5 hour, PEG-coated AV-resinates were obtained by drying the suspension in the oven at 40°C.

Ten grams PEG-coated AV-resinates and 0.4 g PEG400 were gradually added to 80 mL 2.5% (w/v) carbopol 934 ethanol solution, which was agitated until well dispersed[19]. Then the suspension was added into the mixture consisting of 300 mL liquid paraffin and 20 mL Span80 drop by drop to form a suspension. The suspension was kept stirring at 40°C for 3 hours. The AV-resinate microspheres were then harvested by filtration with a 400-mesh sieve, washed with petroleum benzene, and dried at 40°C for 2 hours.

Particle size analysis by dynamic light scattering

The mean particle size of the microspheres was measured using a laser light scattering particle size analyzer (LS230, Beckman Coulter, Miami, FL, USA) according to user's manual.

Determination of drug content in the microspheres

The AV amount in the microspheres was determined by suspending 100 mg AV-loaded microspheres in 100 mL HCl solution (1 mol/L) under magnetic stirring for 10 hours at 65°C. The solution was then filtered, and the amount of AV in the filtrate was determined using UV spectroscopy at 252 nm.

In vitro drug release

In vitro drug release investigations were carried out following the USP paddle (apparatus II) method by a ZRS-8G Intelligent Dissolution Tester Apparatus (Tian Jin University Radio Factory, Tian Jin, China) at a paddle speed of 75 rpm. Briefly, 0.1 + 0.05 mol/L NaCl at 37 ± 0.1°C was used as the dissolution medium. Microspheres containing 500 mg AV were accurately weighed according to loading efficiency and suspended in 900 mL of dissolution medium. Five milliliters of dissolution medium was withdrawn at different intervals (1, 2, 4, 6, 8, 10, and 12 hours) and filtered. The amount of drug released in the filtrate was measured by UV spectrophotometry at 252 nm.

In vivo evaluation of mucoadhesive properties in rats

Eighteen rats were fasted overnight. Each rat was orally administered with 100 granules of the AV mucoadhesive

microspheres. After administration, the rats were kept fasted until they were sacrificed after 2, 4, and 6 hours (six rats at each time point). The microspheres remaining in the GI tract were counted.

In vivo evaluation of mucoadhesive properties in beagle dogs

Two milliliters of carbopol 934-alcohol solution (1.5%) was mixed with 1 mL of 0.1 mol/L HCl containing 1 mg stannous chloride and 1 mg Vitamin C. Ten milliliters of sodium pertechnetate solution equivalent to radioactivity of 100 mci was added and kept at 90°C for 10 minutes. The $^{99m}TcO_4$-labeled carbopol 934 was then used for the microspheres preparation.

The beagle dogs were fasted for 12 hours with free access to water and given $^{99m}T_cO_4$-labeled microspheres loaded with 500 mg AV by oral administration[20]. The 140 keV gamma rays emitted by technetium ($^{99m}T_c$) were imaged. The gamma images were recorded using a real-time imaging system (Millennium VG hawk-eye, Fairfield, CT, USA) and images were acquired at suitable time intervals.

In vivo study

The in vivo evaluation was performed by a crossover treatment in six healthy beagle dogs (weighing 20 ± 2.5 kg) with a 7-day washout period. The beagle dogs were fasted overnight for at least 12 hours with free access to water. Food was not allowed until 4 hours after oral administration[21,22]. The gastric mucoadhesive sustained-release AV-resinate microspheres were used as test preparation. The conventional AV tablets (20080304, 500 mg AV/tablet, Shi Chuan Xin Hua Pharmaceutical Factory, Chengdu, China) were used as a reference preparation. Both preparations contained a dose of 500 mg AV. The test and reference preparation was orally administered to beagle dogs along with 50 mL of water. All studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication No. 85-23, revised in 1985) and were approved by the Department of Laboratory Animal Research at Shenyang Pharmaceutical University. Five milliliters of blood samples were taken at the following time points: 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 hours after oral administration. The blood samples were then centrifuged at 1200 × *g* for 10 minutes. Plasma was harvested and stored at −20°C until further use.

Analysis of AV in plasma samples

The AV amount in plasma was determined by the following procedures. Plasma samples (400 μL) were mixed with 70 μg/mL ganciclovir (internal standard) solution and vortexed for 5 minutes. Twenty percent of $HClO_4$ (200 μL) was added to each sample which was then centrifuged at 13,000 × *g* for 10 minutes. The supernatant was then analyzed using an HPLC system, which was equipped with an LC-10AT HPLC pump (Shimadzu), a SPD-10AVP UV Spectrometer detector (Shimadzu), and a Diamonsil C_{18} column (200 × 4.6 mm, 5 μm particle size; Dikma, Beijing, China). The sample injection volume was 20 μL and the UV detection wavelength was 275 nm. Analysis was performed at 30°C using a mobile phase (water : methanol : glacial acetic acid, 98 : 2 : 0.4, v/v) at a flow rate of 1.0 mL/min. Analysis methods were validated according to the established international guidelines and requirements (Validation of analytical Methods: Definitions and Terminology, ICH Topic Q2A, and Validation of Analytical Procedure: Methodology, ICH Topic Q2B). No interfering peaks were detected at the retention times of AV (9.9 minutes) and ganciclovir (13.3 minutes). A linear correlation ($r > 0.999$) was obtained between the ratio of the peak areas of AV to that of the internal standard and AV concentration between the range 0.1–20 μg/mL. The limit of quantification (10× background noise) was 1 ng. Precision and accuracy of the method were evaluated at concentration of 20, 2, and 0.1 μg/mL. Precision of the method was assessed on the basis of the coefficient of variation in quality control samples and accuracy was calculated as the bias% of these and 2.4–7.0% at all concentration. The bias% of the intra- and interday accuracy was 1.1–2.2% and 0.7–0.9%. No decrease in the content of quality control samples was observed in the freezer.

Pharmacokinetics Study

The pharmacokinetic parameters including the maximum plasma concentration (C_{max}) and time of the maximum plasma concentration (T_{max}) were observed values from the plasma concentration–time curve. The areas under the serum concentration–time curve (AUC_{0-24h}) were calculated by the trapezoidal method. The in vivo drug absorption percentage for the AV microspheres was calculated according to the method of Wagner and Nelson[23]. The in vivo–in vitro correlation for the AV microsphere was obtained from the linear regression analysis between the percentage absorbed in vivo and the percentage released in vitro at the corresponding times. Results from the two preparations were analyzed with the SPSS statistical package using an analysis of variance to assess any significant ($P < 0.05$) difference.

Statistics

Data were obtained at least in triplicate and expressed as mean ± SD. Statistical differences were determined

by student's two-tailed *t*-test. Differences are considered statistically significant at $P < 0.05$.

Results and discussions

Drug absorption in stomach and different intestinal segments in rat

Absorption ratio (%) of AV in the rat's stomach in situ after 3 hours was 9.46 ± 0.62% ($n = 6$). After AV absorption test in rat's intestines in situ for 3 hours, the absorption ratio (%) of AV in duodenum, jejunum, ileum, and colon were 20.22 ± 1.50%, 15.7 ± 1.33%, 9.15 ± 1.01%, and 4.59 ± 0.48%, respectively. It was found that the absorption rate of AV was higher in stomach, duodenum, and jejunum of rat's GI tract.

For drugs that were mainly absorbed in the stomach or in the upper and middle parts of the intestine, the drug delivery system should be designed to maximize the drug retention time in the upper GI tract. Because AV was more efficiently absorbed in the upper and middle segments of the small intestine, one potential way to increase its bioavailability is to increase its retention time in the GI tract.

AV solubility in different medium

The solubility of AV in different tested medium is shown in Table 1. The result showed that AV was less soluble in water, but its solubility increased significantly in acidic solution. This could be explained by the fact that AV could be ionized in the acid solution.

The results obtained from AV solubility study demonstrated that AV was slightly soluble in water, but its solubility could increase significantly in acid medium. Hence acid medium was chosen to prepare the AV-resinates. However, the H^+ in acid medium could compete the active site with AV and result in decrease of resin exchange/loading capacity. In this study, HCl at an optimized concentration of 0.01 mol/L was used for AV-resinate preparation.

Particle size analysis

The size distribution of the microspheres is shown in Figure 1. The average particle diameter was 115.3 μm. According to the Stoke theory, the particle size would enhance the physical stability of the suspension made of microsphere for clinical application.

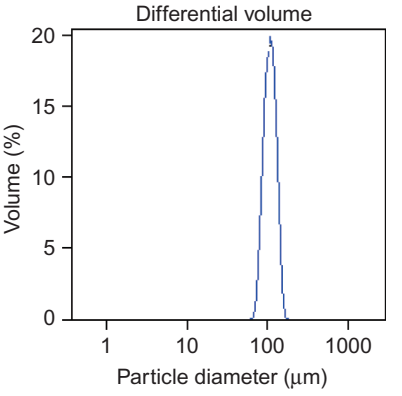

Figure 1. The size distribution.

Determination of drug content in the microsphere

The drug-loading amount in the microsphere was 33.3 ± 0.7% ($n = 6$), as determined by UV absorption at 252 nm. Previous study[24] showed that the exchange capacity of the used ion-exchange resin was 4.87 ± 0.04 mmol/g, indicating the theoretical maximum drug-loading ratio of the AV-resinate is 52.5% (w/w). The drug-loading ratio in this study is lower than the theoretical value, which could be explained by the competition between AV and H^+ in the drug resinates preparation process.

In vitro drug release

The in vitro drug release result is shown in the Figure 2; the drug was released in a sustained manner for 12

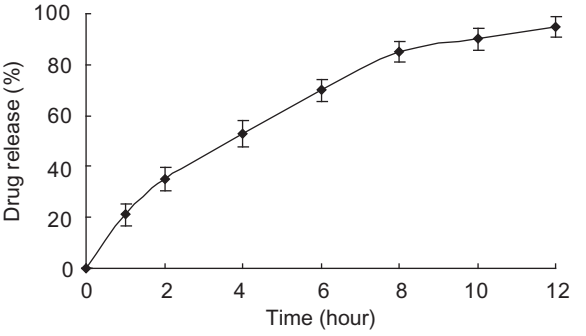

Figure 2. The drug release from the AV bioadhesive microspheres ($n = 6$).

Table 1. Solubility of AV in different mediums.

Medium	Water	0.005 mol/L HCl	0.01 mol/L HCl	0.1 mol/L HCl	0.5 mol/L HCl
Solubility (mg/mL)	0.94 ± 0.08	6.43 ± 0.73	10.78 ± 1.02	16.44 ± 1.01	23.28 ± 1.53

hours, more than 90% of loaded drug was released after 12 hours.

The dissolution media used should be similar to the digest fluid in GI tract. The drug release process is an ion-exchange process from the drug-resinate. The ion concentration of electrolytes in the digest fluid was ~0.15 mol/L. Because the microspheres were mucoadhesive to the stomach (pH 1), 0.1 mol/L HCl and 0.05 mol/L NaCl were used as the dissolution media.

In vivo evaluation of mucoadhesive properties in rats

As shown in Figure 3, it was found that about 60% of the microspheres remained in rat's stomach 6 hours after intragastric administration, whereas normal food retention time in stomach is about 2–4 hours. The results indicated that carbopol coated on the microspheres induced the adhesion to the gastric mucosa, which increased the retention time of the microspheres in the stomach. The adhesive force between the polymer and mucosa layer was reported to depend on the distribution state of carbopol in the microspheres, that is, as a coating layer or being dispersed in the microspheres[25]. Both in vitro and in vivo tests showed that the carbopol as a coating layer could adhere to the mucosa more strongly. In this study, the in vivo mucoadhesive tests showed that microspheres had good adhesive effects on gastric mucosa.

In vivo evaluation of mucoadhesive properties in beagle dogs

Gamma scintigraphy was applied to assess the gastroretention of the microspheres in healthy beagle dogs. Technetium was selected to radiolabel the microspheres because of its short half-life of 6 hours and small amount of electron emission. Sufficient stability of technetium allowed successive gamma imaging for the duration of the study[26]. Gamma scintigraphic images of the fasted beagle dogs showed that most of microspheres were retained in the stomach after 6 hours (Figure 4), which showed a significant gastroretentive profile of the microspheres and a strong interaction between the microspheres and the mucosa.

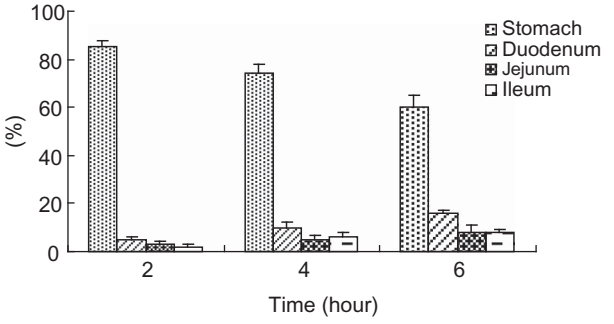

Figure 3. The in vivo retentions results of AV bioadhesive microspheres in rats. Each point represents the mean ± SD ($n = 6$).

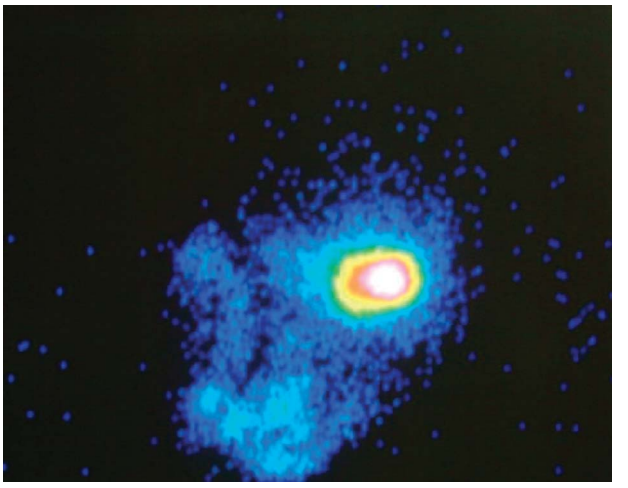

Figure 4. The γ-scintiscan photograph of AV bioadhesive microspheres in beagle dog.

In vivo study

Figure 5 shows the AV plasma concentration–time profiles of test and reference preparation. Table 2 summarizes the pharmacokinetic parameters. Table 3 summarizes the relative bioavailability of the test preparations, obtained using the following equation:

$$F_r = \frac{AUC_{0-24}(\text{test})}{AUC_{0-24}(\text{reference})}.$$

The in vivo–in vitro correlation results were as follows:

$$Y = 1.1962 \times X - 2.1266 \ (r^2 = 0.9574),$$

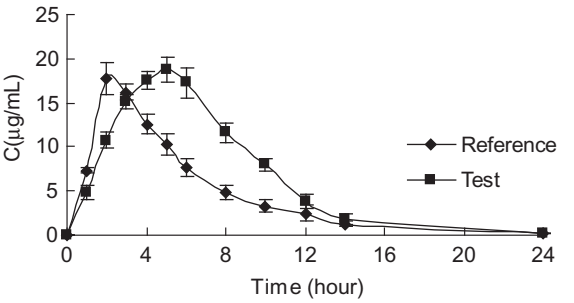

Figure 5. Plasma concentration–time curve of AV following oral administration of reference and test preparation. Each point represents the mean ± SD ($n = 6$).

Table 2. Pharmacokinetic parameters of AV after a single dose of testing preparation and reference preparation.

Parameter	Reference preparation	Test preparation	ANOVA
$t_{1/2(ke)}$ (hours)	2.90 ± 0.21	3.02 ± 0.084	$P > 0.05$
k_e (h^{-1})	0.24 ± 0.017	0.230 ± 0.006	$P > 0.05$
T_{max} (hours)	2.33 ± 0.52	5 ± 0.63	$P < 0.05$
C_{max} (μg/mL)	18.13 ± 1.43	19.29 ± 1.03	$P > 0.05$
AUC_{0-24h} (μg h/mL))	105.17 ± 13.53	152.02 ± 14.20	$P < 0.05$
$AUC_{0-\infty}$ (μg h/mL)	105.68 ± 13.54	153.21 ± 14.30	$P < 0.05$
MRT (hours)	5.68 ± 0.28	6.84 ± 0.19	$P < 0.05$

Table 3. Relative bioavailability of AV after a single oral dose of two preparations ($n = 6$).

Subject	Test AUC_{0-24h} (μg h/mL)	Reference AUC_{0-24h} (μg·h/mL)	Relative bioavailability (%)
Dog A	150.15	104.22	144
Dog B	140	93.05	150
Dog C	165.66	117.32	141
Dog D	138.08	87.49	158
Dog E	145.37	106.25	137
Dog F	172.89	122.66	141
Mean ± SD	152.02 ± 14.20	108.04 ± 13.01	145 ± 0.08

where Y is fraction absorbed in vivo and X represents fraction released in vitro.

The comparison of parameters with the two preparations showed no significant differences for C_{max} but indicated significant difference for t_{max} and AUC_{0-24h}. The t_{max} increased from 2.33 (reference) to 5 hours (test), indicating a sustained-release property in vivo. Meanwhile, the relative bioavailability of test preparation increased significantly by 45%. And a good correlation between in vivo drug absorption and in vitro drug release was obtained in the AV microsphere. The above results showed that the mucoadhesive AV-resinate microspheres increased the transit time in the stomach and thus increased the absorption of the AV.

Conclusions

In this study, a novel gastric mucoadhesive sustained-release AV-resinate microsphere was prepared. Studies showed that AV has a better absorption ratio in the stomach and upper intestine. The gastric mucoadhesive sustained-release AV-resinate microspheres showed a sustained-release profile and increased retention time in the stomach in vitro. The in vivo study also showed a sustained-release profile with 45% higher bioavailability as compared to conventional AV tablets.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Massimiliano G, Patrizia C, Maurizio R, Philip SB, Alan GEW, Mark ES, et al. (2007). Evaluation of a basic physiologically based pharmacokinetic model for simulating the first-time-in-animal study. Eur J Pharm Sci, 31:190–201.
2. Suresh K, Ritesh J, Deep K, Sudharshan H, Ashim KM. (2008). Pharmacokinetics of amino acid ester prodrugs of acyclovir after oral administration: Interaction with the transporters on Caco-2 cells. Int J Pharm, 362:93–101.
3. Tory P, Johnson RF, Melissa M, Timothy PB, Barry JM. (2007). Development of an aciclovir implant for the effective long-term control of herpes simplex virus type-1 infection in Vero cells and in experimentally infected SKH-1 mice. Int J Antimicro Ag, 30:428–35.
4. Fletcher C, Bean B. (1985). Evaluation of oral acyclovir therapy. Drug Intell Clin Pharm, 19:518–24.
5. Zeljka P, Natasa SB, Jelena FG, Anita M, Ivan J. (2005). Development and in vitro evaluation of a liposomal vaginal delivery system for acyclovir. J Control Release, 106:34–43.
6. Conti B, Bucolo C, Giannavola C, Puglisic G, Giunchedia P, Contea U. (1997). Biodegradable microspheres for the intravitreal administration of acyclovir: in vitro/in vivo evaluation. Eur J Pharm Sci, 5:287–293.
7. Lawa SL, Huang KJ, Chiang CH. (2000). Acyclovir-containing liposomes for potential ocular delivery corneal penetration and absorption. J Control Release, 63:135–40.
8. Alsarra IA, Hamed AY, Mahrous GM, Maghraby GMEI, Al-Robayan AA, Alanazi FK. (2009). Mucoadhesive polymeric hydrogels for nasal delivery of acyclovir. Drug Dev Ind Pharm, 35:352–62.
9. Rao CGG, Motiwale AV, Satyanarayana D, Subrahmanyam EVS. (2004). Formulation of taste masked oral microsphere of quinine sulphate by complexation. Indian J Pharm Sci, 66: 329–31.
10. Atyabi F, Sharma HL, Mohammad HAH, Fell JT. (1996). Controlled drug release from floating ion exchange resin beads. J Control Release, 42:25–8.
11. Hideki I, Kazuhiro F, Moji CA, Yoshinobu F. (2001) Use of ion-exchange resins to prepare 100 μm-sized microspheres with prolonged drug-release by the Wurster process. Int J Pharm, 216:67–76.
12. Plaizier-Vercammen JA. (1992). Investigation of the bioavailability of codeine from a cation ion-exchange sulfonic acid 1. Effect of parameters. Int J Pharm, 85:45–50.
13. Liu HF, Su XY,Li X, Zhao X, Zang L, Pan WS. (2006). Development of prolonged release microspheres of metformin hydrochloride using ion exchange resins. J Chin Pharm Sci, 15:155–61.
14. Ceschel GC, Bergamante V, Calabrese V, Biserni S, Ronchi C, Fini A. (2006). Design and evaluation of controlled release mucoadhesive tablets containing chlorhexidine *in vitro*. Drug Dev Ind Pharm, 32:53–61.

15. Lu GW, Jun HW. (1998). Diffusion studies of methotrexate in Carbopol and Poloxamer gels. Int J Pharm, 160:1–9.
16. Zhang XN, Chen J, Zhang Q. (2003). Study on the release of albendazole nanoparticles in vitro and its correlation with uptake in stomach and intestinal absorption kinetics in rats. Chin Pharm J, 38:932–5.
17. Michel C, Aprahamian M, Defontaine L, Couvreur P, Damgé C. (1991). The effect of site of administration in the gastrointestinal tract on the absorption of insulin from nanocapsules in diabetic rats. J Pharm Pharmacol, 43:1–5.
18. Akkaramongkolporn P, Ngawhirunpat T. (2003). Dual ambroxol and chlorpheniramine resinates as an alternative carrier in concurrent resinate administration. Phamazie, 58:195–9.
19. Perumal D. (2001). Microencapsulation of ibuprofen and Eudragit®RS 100 by the emulsion solvent diffusion technique. Int J Pharm, 218:1–11.
20. Fu J, Sun X, Zhang ZR. (2002). The investigation of bioadhesive property of Carbomer 934 by Gamma Camera in vivo. J Biomed Eng, 19:423–5.
21. Jankowski A, Jankowska AL, Lamparczyk H. (1998). Determination and pharmacokinetics of acyclovir after ingestion of microsphere form. J Pharm Biomed Anal, 18:249–54.
22. Grazia S, Md EA, Daniella W. (2004). Pharmacokinetics of acyclovir in rabbit skin after IV-bolus, ointment, and iontophoretic administrations. Int J Pharm, 274:201–11.
23. Wagner JG, Nelson E. (1964). Kinetic analysis of blood levels and urinary excretion in the absorptive phase after single dose of drug. J Pharm Sci, 53:1292–1243.
24. Liu HF, Zang L, Sun XY, Zhang S, Pan WS. (2005). Study on the basic physicochemical properties of the new excipient-sodium polystyrene sulfonate. Chin J New Drug, 14:1007–9.
25. Akiyama Y, Nagahara N, Kashihara T, Hirai S, Toguchi H. (1995). *In vitro* and *in vivo* evaluation of mucoadhesive microspheres prepared for the gastrointestinal tract using polyglycerol esters of fatty acids and a poly(acrylic acid) derivative. Pharm Res, 12:397–405.
26. Yao HM, Xu L, Han F, Che X, Dong Y, Wei M, et al. (2008). A novel riboflavin gastro-mucoadhesive delivery system based on ion-exchange fiber. Int J Pharm, 364:21–6.