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**RESEARCH ARTICLE**

# Influence of admixed citric acid and physiological variables on the vinpocetine release from sodium alginate compressed matrix tablets

Shufang Nie[1,2], Jie Wu[1], Hui Liu[3], Weisan Pan[2], and Yanli Liu[2]

*[1]Department of Pharmaceutical Engineering, Wuhan Bioengineering Institute, Yangluo Economic Development Zone, Wuhan, China, [2]Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, China, and [3]Department of Pharmacy, Wuhan Gerneral Hospital, Wuhan, China*

**Abstract**

In this study, the controlled release matrix tablets of vinpocetine were prepared by direct compression using sodium alginate (SAL) as hydrophilic polymer and different amounts of citric acid as hydrosoluble acidic excipient to set up a system bringing about zero-order release of this drug in distilled water containing 0.5% sodium dodecyl sulfate. At the critical content of admixed citric acid (60 mg/tab.), the lowest drug-release rate was observed. In order to explain the effect of this critical content on drug-release rate from SAL matrices, investigation of the possibility of interaction of citric acid with SAL was performed using differential scanning calorimetric analysis and infrared analysis, which confirmed the existence of direct citric acid-SAL interaction when these two excipients came in contact with water. A zero-order drug-release system could be obtained by regulating the ratio of citric acid-to-SAL and the capacity of this system in controlling drug-release rate depended on the extent of interaction between citric acid and SAL. It is worth noticing that pH and the ionic strength of the dissolution medium were found to exert an influence on the drug-release performance of SAL tablets.

**Keywords:** Vinpocetine, citric acid, sodium alginate, zero-order release, matrix tablets

## Introduction

Vinpocetine was introduced into the clinical practice some 20 years ago in Hungary for the treatment of disorders and related symptoms. Since then, vinpocetine has become a reference compound in the pharmacological research of cognitive deficits caused by hypoxia and ischemia as well as in the cellular and biochemical investigations related to cyclic nucleotides[1,2]. In the development of cerebrovascular medicine the constant searches are needed not only for new and more powerful drugs, but also for more effective formulations of already known drugs. Because of the short half-life of 2–4 h[3], frequent dosing of vinpocetine is necessary to maintain the therapeutic effect. This makes vinpocetine a good candidate for a sustained release system. Sustained release dosage forms cannot only significantly improve patient compliance, especially in case of drug chronic use, but also reduce the total dosage of administered drug and, consequently, the possible side effects.

The use of nature hydrophilic polymers as drug carrier has received considerable attention in the past few years, especially from the viewpoint of cost, environmental pollution and safety. Sodium alginate (SAL), a water-soluble salt of alginate acid, is a natural polysaccharide extracted from marine brown algae, which composed of 1,4-linked β-D-mannuronic acid and α-L-guluronic acid residences. SAL has been widely used as a stabilizing, thickening, dispersing, and gelating agent for food. Recently, SAL has been used as a matrix for sustained release of drug since it has ability to react with divalent ions (such as calcium chloride, calcium gluconate) to give water-insoluble cross-linked matrices in aqueous medium[4,5]. It is well known that interactions of excipient–excipient have been extensively reported in the literature, especially

*Address for Correspondence*: Shufang Nie, Department of Pharmaceutical Engineering, Wuhan Bioengineering Institute, Han-Shi Road 1, Yangluo Economic Development Zone, Wuhan, China. Tel.: +86 13297969709. E-mail: niesf77@163.com

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during preformulation studies[6]. Some interaction between excipients of matrix tablets may not be evident in the solid state, but cannot be avoided when the dosage form comes in contact with the dissolution medium, which can actually adjust the medicine release rate from this kind of matrices to satisfy special requirement in controlled release systems. An interaction under these conditions, whether physical through hydrogen bonding or chemical through the formation of insoluble complexes, may affect the rate and extent of drug release.

In this study, zero-order release of vinpocetine from matrix tablets composed of SAL and citric acid were prepared and the interaction of SAL and citric acid was investigated using differential scanning calorimetric (DSC) analysis and infrared (IR) analysis to explain the effect of admixed citric acid on drug release from SAL matrices. Few information about the effect of interaction of citric acid and SAL on the drug release has been available. Therefore, it was the objective of this work to study the effects of such interaction on the design of zero-order release systems.

## Materials and methods

### Materials

The following materials were used: Vinpocetine was a gift from East-North Pharmaceutical Company (Shenyang, China); SALs (Keltone LVCR (54 kDa, M/G ratio 1.5) and Keltone HVCR (160 kDa, M/G ratio 1.5), NF) were received from ISP Co. (New Jersey, USA); hydroxypropyl methylcellulose (HPMC K4M) was a gift from Colorcon Co. (Shanghai, China); microcrystalline cellulose (Avicel PH101) was a gift from FMC Corporation, Philadelphia, PA; anhydrous citric acid was purchased from the Third chemical Manufacturing of Shenyang (Shenyang,China). The other excipients and chemicals used were of analytical reagent grade.

### Methods

#### *Solubility studies*

The solubility of vinpocetine was investigated in HCl solution (pH1.2), citric acid/$NaH_2PO_4$ buffer (pH4.0), and $KH_2PO_4$/NaOH buffer (pH6.8) at room temperature, respectively,. As the original buffers used have slightly different levels of ionic strength, sodium chloride was added to adjust the ion concentrations in dissolution media to the same level ($\mu \approx 0.1$).The solubility of vinpocetine in aqueous solution containing different concentrations of citric acid (0–3%, w/v) was also examined at room temperature.

For the determination of the saturation solubility, excess amounts of drug were added to 20 ml solution and mechanically shaken until equilibrium (about 72 h). Then, the filtered solutions were analyzed by high-performance liquid chromatography after diluting with the mobile phase. Vinpocetine was fractionated on a Hypersil ODS column (15 cm × 4.6 mm, ID with 5 μm packing material) with detection at 273 nm using a mobile of methanol-water (80:20, with 0.3% acetate acid). Three replicates have been made for each experience.

### Preparation of compressed matrices

SAL was used to produce matrices containing 15 mg vinpocetine loading in different ratios of SAL: citric acid. The compositions of different SAL formulations were shown in Table 1. In order to compare the effect of citric acid on the drug release, HPMC (K4M) was also used to produce matrices containing 15 mg vinpocetine loading in different ratios of vinpocetine: citric acid as that for SAL matrices. The compositions of tablet formulations were shown in Table 2.

The drug and the corresponding quantities of other components (SAL or K4M, citric acid, PH101, and magnesium stearate) were mixed manually completely and then passed through an 80-mesh sieve for three times. The matrix tablets were prepared by direct compression in a single punch tablet machine (TDP single tablet machine, The first pharmaceutical manufacturing of Shanghai) using 9-mm flat-faced punch for SAL matrices and 8-mm for HPMC matrices. Tablets with hardness values of 6–8 kg/cm$^2$ (determined by Monsanto hardness tester, Wuhan Aisi Pei Scientific Instruments Co., Ltd.) were prepared by applying suitable compression

Table 1. Compositions of different SAL matrices.

| Formula | Vinpocetine (mg) | SAL(H)* (mg) | SAL(L)* (mg) | Citric acid (mg) | PH101 (mg) | Mg stearate (mg) |
|---|---|---|---|---|---|---|
| H1 | 15.0 | 200.0 | — | — | 75.0 | 2.0 |
| H2 | 15.0 | 200.0 | — | 15.0 | 60.0 | 2.0 |
| H3 | 15.0 | 200.0 | — | 30.0 | 45.0 | 2.0 |
| H4 | 15.0 | 200.0 | — | 45.0 | 30.0 | 2.0 |
| H5 | 15.0 | 200.0 | — | 52.5 | 22.5 | 2.0 |
| H6 | 15.0 | 200.0 | — | 60.0 | 15.0 | 2.0 |
| H7 | 15.0 | 200.0 | — | 67.5 | 7.5 | 2.0 |
| H8 | 15.0 | 200.0 | — | 75.0 | — | 2.0 |
| L1 | 15.0 | — | 200.0 | — | 75.0 | 2.0 |
| L2 | 15.0 | — | 200.0 | 30.0 | 45.0 | 2.0 |
| L3 | 15.0 | — | 200.0 | 45.0 | 30.0 | 2.0 |
| L4 | 15.0 | — | 200.0 | 60.0 | 15.0 | 2.0 |
| L5 | 15.0 | — | 200.0 | 75.0 | — | 2.0 |

SAL(H)* = high viscosity sodium alginate; SAL(L)* = low viscosity sodium slginate.

forces. The tablet weight was 292 mg ± 1% and 202 mg ± 2% for SAL matrices and HPMC matrices, respectively.

### Dissolution methodology

*In vitro* release tests were carried out in 500 ml dissolution medium containing 0.5% sodium dodecyl sulfate (SDS) (in order to maintain sink condition) at 37 ± 0.5°C using USP paddle (apparatus II) method with a ZRS-8G intelligent Dissolution tester (Tianjin university Radio Factory, Tianjin, China) at a speed of 50 rpm. Six sinkers were used in order to reduce the variability due to hydrodynamic conditions of the test and to overcome the problem due to possible sticking of the gelled matrix on the wall of the dissolution container. Samples (5.0 ml) were withdrawn at predetermined time intervals, filtered and analyzed spectrophotometrically at wavelength of 268 nm (UV spectrophotometer, model UV-9100, Beijing Ruili analysis instrument Co. Beijing, China). Fresh dissolution medium (5.0 ml) was added to maintain a constant volume. Quantitative measurements of drug by spectroscopy were performed by comparing each absorbance with that of a standard curve with acceptable correlation coefficient.

The effect of pH on the drug-release performance of SAL tablets was studied using a series of dissolution media, produced from the simulated gastric fluid without pepsin (pH1.2) and buffers of citric acid/$NaH_2PO4$ (pH4.0), and $KH_2PO_4$/NaOH (pH6.8). Sodium chloride was added to adjust the ion concentrations in dissolution media to the same level ($\mu \approx 0.1$) in order to exclude the interference of the effect of ionic strength on drug release. The influence of the ionic strength of the dissolution medium on the drug-release performance of SAL tablets was also studied within a range of ionic strength of 0–0.2. The ionic strength of solutions used was regulated by sodium chloride. All release tests were run in triplicate.

### Gravimetric erosion studies

Matrix erosion studies were conducted for SAL(H) (H4, H6, H8) and SAL(L) (L3,L4,L5) formulas in 500 ml distilled water containing 0.5% SDS at 37 ± 0.5°C using a method similar to that described for drug dissolution tests. Matrix erosion studies also conducted for pure SAL(H) matrices (200 ± 2 mg/tab.) in 500 ml distilled water containing 0, 0.25, 0.5 or 1.0% citric acid solution in order to investigate the effect of citric acid concentration on erosion rate of SAL matrices. Six preweighed stainless sinkers were used and at different time intervals, each tablet was removed and placed in a hot air oven at 45 ± 2°C. In all cases, constant weight was achieved within 24 h and this reading, compared to each sinker weight, gives the remaining weight of tablet. Again, the average of three measurements was taken.

### Preparation of samples for DSC and IR studies

Powders of citric acid and SAL(H) (total amount 2.6 g) were dissolved in distilled water (50 ml) at the citric acid: SAL(H) ratio of 3:10 (w/w), and the solvent was then evaporated at 40°C. The interaction product was ground and dried at 40°C for 24 h under reduced pressure. The physical mixtures were prepared by simply mixing the dried citric acid and SAL(H) with the ratio of 3:10 (w/w) using a mortar and a pestle.

### DSC analysis

DSC curves were determined with a DSC instrument (DSC-60, Shimadzu, Japan).Samples of the pure anhydrous citric acid, SAL(H), their physical mixtures and their interaction products were hermetically sealed in a flat-bottomed aluminum pan. Samples were heated over the temperature range 25–350°C with the heating rate of 10°C/min under nitrogen gas flowed at a rate of 40 ml/min.

### IR analysis

IR spectra of pure citric acid and SAL(H), as well as their physical mixtures and interaction products, were recorded with an IR spectrophometer (Bruker IFS55) in the range 4000–250 $cm^{-1}$ at ambient temperature (25°C)

## Results and discussion

### Solubility studies

It was evident that the solubility of vinpocetine was remarkably dependent on the pH value of medium, which was dramatically increased when lowered the pH value (Table 3). On the other hand, there was a linear relationship($r = 0.99$) between the solubility of vinpocetine and the concentration of citric acid in distilled water at room temperature(as shown in Figure 1),which suggesting that citric acid could be used as an acidifier in matrix to improve the drug-release rate.

### Influence of citric acid contents on the drug release from SAL matrices

A comparison of the release profiles of matrices containing different amounts of citric acid was showed in Figure 2A and 2B. The amounts of citric acid in the range of 0–75 mg/tab. significantly affected the dissolution process, while keeping the drug and polymer content constant. For

Table 2. The compositions of different HPMC matrices.

| Formula | Vinpocetine (mg) | K4M (mg) | Citric acid (mg) | PH101 (mg) | Mg stearate (mg) |
|---|---|---|---|---|---|
| K1 | 15 | 75 | 15 | 95 | 2 |
| K2 | 15 | 75 | 30 | 80 | 2 |
| K3 | 15 | 75 | 45 | 65 | 2 |
| K4 | 15 | 75 | 60 | 50 | 2 |
| K5 | 15 | 75 | 90 | 20 | 2 |

matrices composed of either high viscosity or low viscosity SAL, the addition of citric acid could produce more complete drug release at 12 h comparing to that of the formula H1 and L1 (containing no citric acid), in which <80% drug could release. Low viscosity SAL matrices induced faster release rate of drug than high viscosity SAL matrices. On the other hand, when the amount of citric acid increased to 60 mg/tab. (citric acid: SAL 3:10), the lowest drug-release rate was obtained no matter which viscosity grade SAL was used. So it implied there must be a critical amount of citric acid added to the SAL matrices, below or beyond which faster drug-release rate could be obtained.

Table 3. The pH of medium on vinpocetine solubility ($n=3$).

| Medium | Solubility of vinpocetine (mM) |
|---|---|
| HCl solution (pH 1.2) | 31.346 ± 0.690 |
| Citric acid/$NaH_2PO_4$ buffer (pH 4.0) | 6.595 ± 0.790 |
| $KH_2PO_4$/NaOH buffer (pH 6.8) | 0.025 ± 0.011 |
| Distilled water | 0.030 ± 0.009 |

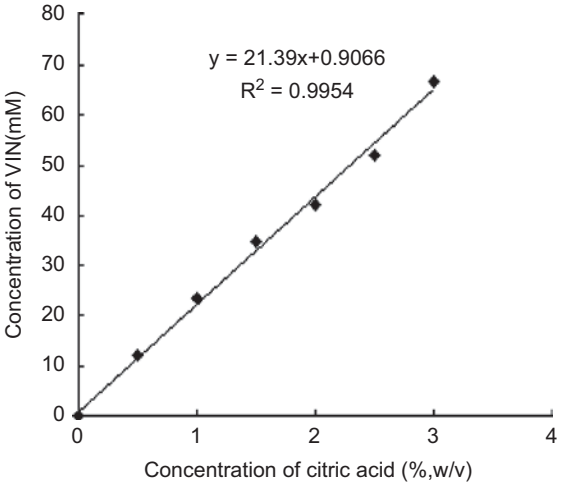


Figure 1. Mean solubility of VIN as a function of CA concentration in distilled water. ($n=3$)

Interestingly, matrices processing greater proportion of citric acid exhibited a drug-release closer to a zero-order release model up to 12 h.The zero-order regression equation parameter and correlation efficient for each formula release data were showed in Table 4.

In order to explain this unusual release behavior, it should be taken into consideration that the possibility of interaction between citric acid and SAL might exist when matrices come into contact with the dissolution medium. The following experimental techniques, DSC and IR studies, has been carried out to allow us to seek evidence of direct citric acid-SAL interaction for understanding of this release behavior.

## DSC analysis

DSC patterns of citric acid, polymer, their physical mixture, and their interaction product (Figure 3) undoubtedly revealed the interaction of citric acid with SAL, since the endothermic peak of citric acid around 155°C disappeared from the thermogram of interaction products, but

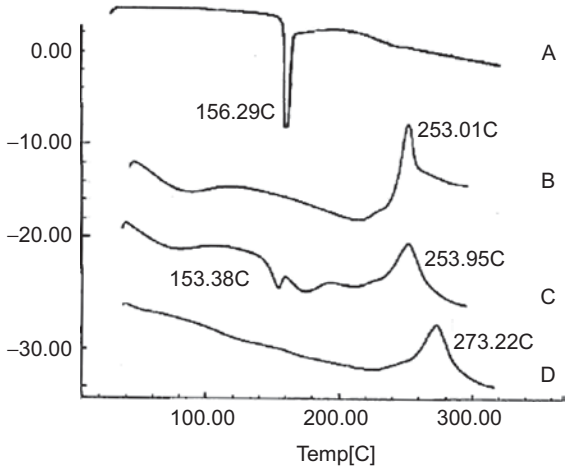


Figure 3. DSC thermogramas of citric acid (A), SAL(H) (B), their physical mixture (C), and their interaction products (D) in 3:10 of citric acid-to-SAL(H).

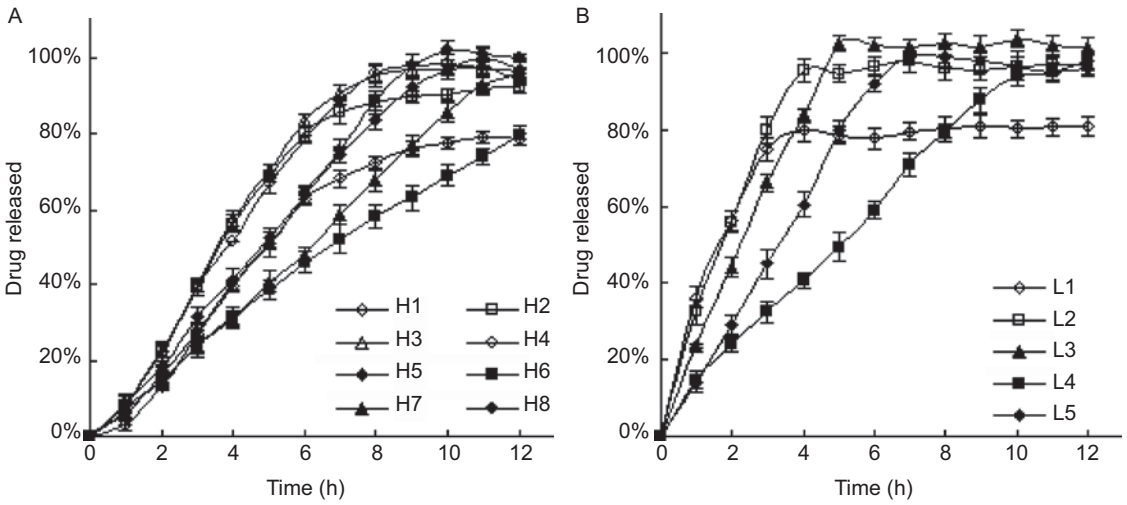


Figure 2. Dissolution of vinpocetine from SAL matrices containing different amounts of citric acid, using distilled water (0.5% SDS) as medium. (A) SAL(H) matrices; (B) SAL(L) matrices.

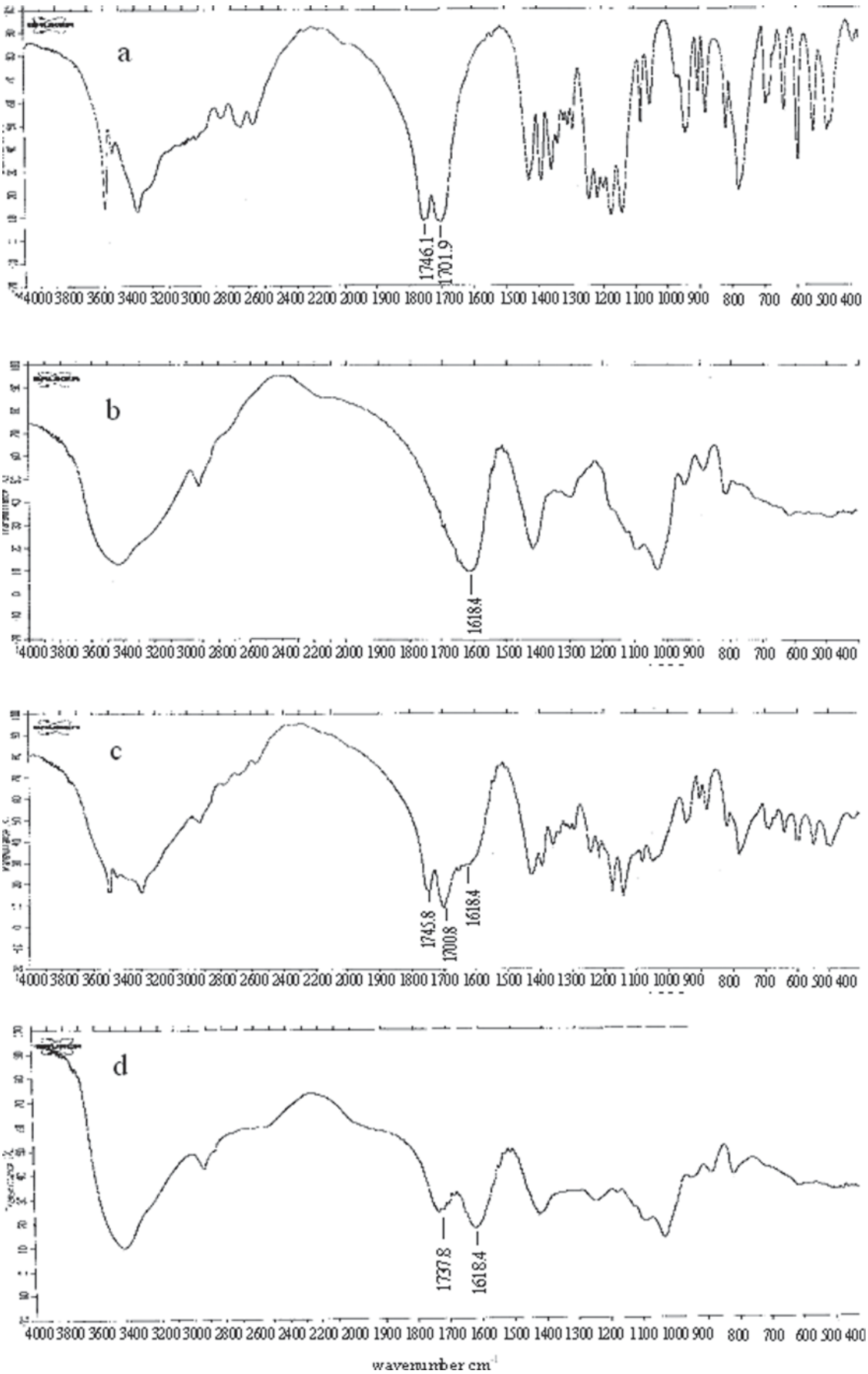


Figure 4. IR spectra of citric acid (A), SAL(H) (B), their physical mixture (C), and their interaction products (D) with 3:10 of citric acid-to-SAL(H).

not from that of the physical mixture. Moreover, the endothermic peak of SAL around 253°C in the thermogram of the physical mixture shifted to 273°C in that of the interaction product, which also verified the interaction between citric acid and SAL.

## IR analysis

SAL has some free hydroxyl groups, which could be easily esterified with aliphatic carboxylic acids. As citric acid has three free carboxyl groups, there was a possibility that carboxyl groups would take part in ester formation. A peak observed around 1618 $cm^{-1}$ for SAL power was due to–$COO^-$, as shown in Figure 4B. Citric acid powder has the carbonyl stretching bands at 1746 $cm^{-1}$ and 1701 $cm^{-1}$ due to monomer and hydrogen bonding dimer (Figure 4A). The new band was observed at 1737 $cm^{-1}$ in the case of citric acid-SAL interaction products (Figure 4D), which would be due to the ester group formed by carbonyl bands of citric acid with the hydroxyl group of SAL. Additionally,

Table 4. Regression equations and correlation efficients of vinpocetine dissolution curves from SAL matrices containing different amounts of citric acid.

| Formula | Regression equation Drug release (%) (y) = aTime(x).+b | *r* |
|---|---|---|
| H1 | Y = 0.096x–0.022 | 0.9632 |
| H2 | Y = 0.121x+0.019 | 0.9575 |
| H3 | Y = 0.130x–0.003 | 0.9728 |
| H4 | y = 0.128x–0.008 | 0.9895 |
| H5 | y = 0.109x–0.021 | 0.9989 |
| H6 | y = 0.074x+0.007 | 0.9965 |
| H7 | y = 0.087x–0.024 | 0.9980 |
| H8 | y = 0.119x–0.072 | 0.9989 |
| L1 | y = 0.150x+0.245 | 0.9451 |
| L2 | y = 0.213x+0.126 | 0.9911 |
| L3 | y = 0.198x+0.046 | 0.9981 |
| L4 | y = 0.090x+0.057 | 0.9977 |
| L5 | y = 0.160x–0.026 | 0.9980 |

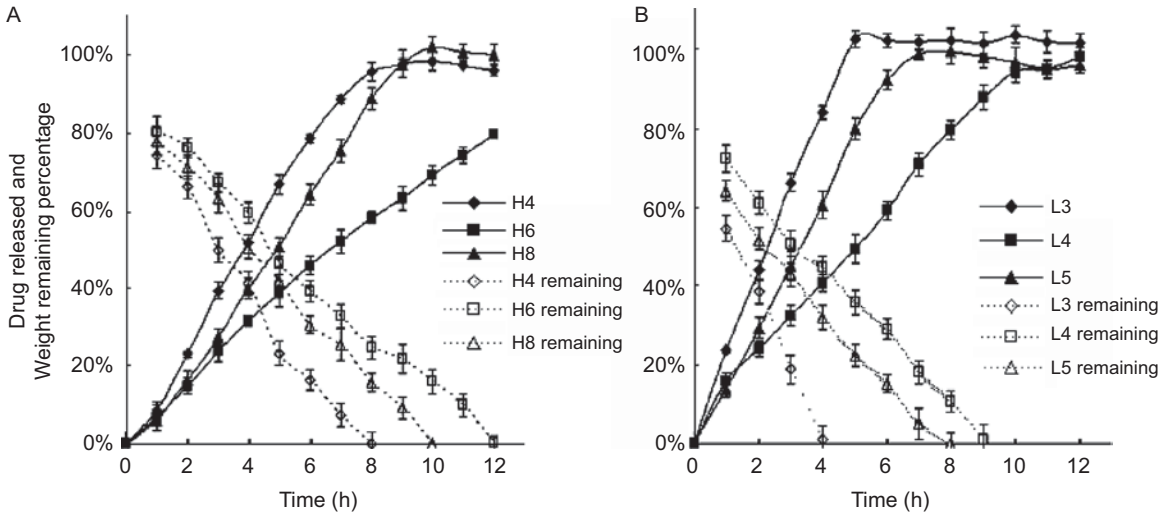


Figure 5. Relationship between the fraction of vinpocetine released and the sodium alginate tablet weight. (A) SAL(H) (H4,H6,H8); (B) SAL(L) (L3,L4,L5).

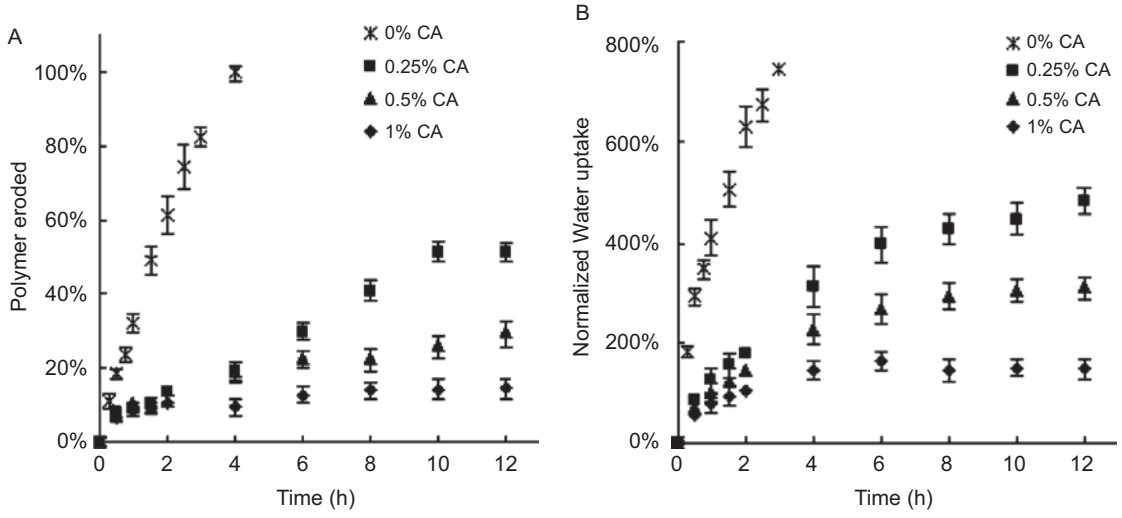


Figure 6. The effect of citric acid concentration in dissolution media on the erosion amount (A) and water uptake amount (B) of pure SAL(H) matrices($n = 3$).

the peak of 1746 $cm^{-1}$ and 1701 $cm^{-1}$ disappeared, which indicated the extent of forming ester groups between citric acid and the polymer should be complete.

The forming of these ester groups might result in a possible decreasing of polymer solubility and, consequently, lowered the capability of water uptake and swelling. This assumption could also be verified from the visual observation that the alginate matrices containing larger amount of citric acid could create a more "tough and rubbery" gel, which was less susceptible to erosion. Figure 5 further demonstrated the relationship between the drug release and tablet weight remaining. The results showed that the lowest erosion rate were found in formulas (H6 and L4) with critical citric acid content due to their highest weight remaining percentage at predetermined time intervals. Lower erosion rate produced lower drug-release rate, which indicated erosion played a crucial role in controlling drug-release rate from SAL matrices.

Figure 6 also demonstrated conclusions drawn above. It was evidence that citric acid concentration in dissolution media had significant effect on the erosion rate and normalized water uptake rate of pure SAL matrices. Lower erosion rate and water uptake rate could be produced by increasing citric acid concentration in solution. As an acidic substance, citric acid could decrease the pH value of solution, which might induce decreased solubility of SAL due to the increasing fraction of unionized carboxyl groups and water discharge as reported by Yotsuyanagi et al.[10] However, as our determined, the pH value of solution containing three different concentration of citric acid was nearly the same (varied from 3.1 to 3.7), which suggested that the citric acid should play a major role rather than pH value in decreasing the erosion rate and water uptake rate of SAL matrices, and consequently provided a more reliable evidence for the existence of citric acid-SAL interaction.

From above mentioned, the critical content effect observed in vinpocetine dissolution studies might be explained on the basis that citric acid, the polymer, and the citric acid-polymer complex were present in matrices during drug-release process. Under the critical level, increasing the citric acid-to-polymer ration was likely to lead to increasing the extent of the insoluble complex formation, which produced a lower amount of the drug released from the matrices. The extent of interaction was the main effect on the drug-release rate. The critical level corresponding to the ratio of citric acid-to-polymer 3:10 might be the optimal ratio at which the largest extent of insoluble complex might be formed. Above this critical level, increasing the amount of citric acid produced increasing release rate of drug from matrices, which suggested that citric acid would not only interacted with polymer, but also played a role as an acid solubilizer in improving the release rate of vinpocetine, which is a weakly basic drug and insoluble in water. This stabilizing effect has been discussed in our recent research about the effect of admixed citric acid on vinpocetine release profile from HPMC matrices (Figure 7), in which no critical

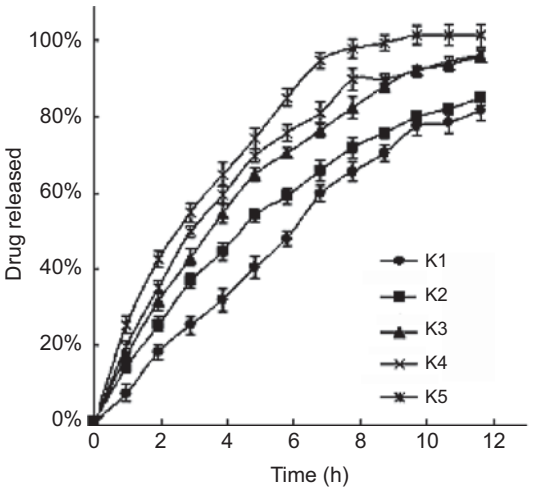


Figure 7. Dissolution of vinpocetine from HPMC matrices containing different amounts of citric acid, using distilled water (0.5% SDS) as medium.

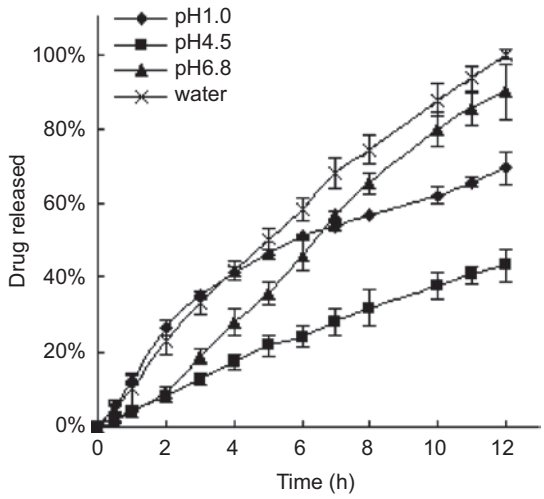


Figure 8. The effect of pH of dissolution medium on the vinpocetine release from SAL matrices (formula H7).

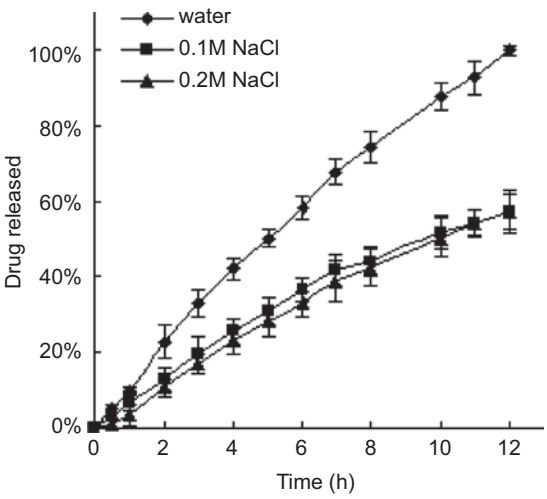


Figure 9. The effect of ionic strength of dissolution medium on the vinpocetine release from SAL matrices (formula H7).

content appeared in the case of increasing the amount of citric acid and insteadly, a good linear relationship($r$ > 0.90) has been observed between the amount of citric acid added to the matrices and the amount of drug release from HPMC matrices.

Comparing to vinpocetine-citric acid-HPMC delivery system[7] which showed anomalous transport drug mechanism no matter how much the citric acid added to the matrices, using SAL(H) or SAL(L) and citric acid as excipients could not only retards drug release, but also provides zero-order release kinetics up to 12 h if the amount of citric acid regulated to a proper level, and the correlation coefficients for most of data were >0.99 (Table 4). So, using SAL as controlling polymer could avoid initial-busting release phenomenon which often takes place in HPMC matrices

On the other hand, in comparison with other hydrophilic matrices by cross-linking of SAL and divalent cations[4,8], the SAL matrices forming gel with aid of citric acid would be advantageous for incorporated in some drugs because cations used for gelation might offer undesirable effects such as salt formation and inactivation caused by metal-drug chelation[5]. Additionally, it seemed to have another potential advantage of controlling release rate of some weak basic drug. Inside SAL matrices, citric acid could be used not only as a cross-linking agent to deceasing drug-release rate, but also as an acidifier to increasing drug-release rate. Which approach would dominate the drug-release process mainly depends on the amount of citric acid added to SAL matrices. So, in this way, the drug-release rate could be adjusted flexibly by regulating the amount of organic acid to satisfy our demand on zero-order drug-release system.

### Influence of pH on the drug release from SAL matrices

The effect of pH of the dissolution medium on the drug-release behavior from matrices (formula H7) was investigated to identify the sensitivity of SAL matrices to the change of physiological pH.

As well known, the swelling, dissolution and erosion of SLA matrix was significantly dependent on the pH value of release medium[9,10]. The results (Figure 8) revealed that pH has a significant influence on the drug-release rate from SAL tablets, which generally followed an order of release in medium of distilled water >pH 6.8>pH 1.0>pH 4.0. The pH-dependence of vinpocetine release could be attributed to both the drug carrier system and the varying solubility of drug itself in dissolution media of different pH. It is known that vinpocetine is a weak basic drug with pH-dependent solubility. The higher solubility in an acidic medium was responsible for the initial faster drug-release rate in 0.1 N HCl than that in pH6.8. However, in hydrochloric acid, it is likely that SAL will be converted to alginic acid, resulting in the formation of a non-swelling, rigid matrix that could release the drug more slowly. It was worth noticing, however, drug release should be faster in the media of pH 4.0 than pH 6.8, nevertheless, the opposite trend of drug-release profiles of matrices obtained. This result might be due to the water-insoluble complex formation by the interaction of SAL inside the matrices and citric acid present in dissolution medium, which adds further support to our suggestion of how citric acid interacts with SAL matrices.

### Influence of ionic strength on the drug release from SAL matrices

The results (Figure 9) revealed that ionic strength also had an effect on drug release from the SAL matrices. Drug release in distilled water, i.e., $\mu = 0$, exhibits the fastest rate when compared with other two drug-release profiles; besides, no significant difference was found in 0.1 M NaCl and 0.2 M NaCl solutions. This result might be due to a possible decrease of water uptake rate and increase of gel strength at the surface of tablets caused by high concentrations of electrolytes, which could result in lower erosion rates of matrices than that in pure water and allowed a slower release in solutions containing sodium chloride.

## Conclusions

This research showed that SAL could be used to modify vinpocetine release rates from hydrophilic matrix tablets prepared by direct compression. Faster drug-release rate has been found from low viscosity SAL matrices than that from high viscosity SAL matrices. In both viscosity SAL matrices, the addition of citric acid led to a significant change in the release capacities of the matrices and zero-order release behavior of drug could be obtained by regulating the amount of citric acid added to SAL matrices. At the critical ratio 3:10 (citric acid-to-SAL), the lowest drug-release rate was observed, below or beyond which faster drug release was obtained. This unusual release behavior could be explained by the interaction between citric acid and SAL taken place when matrix tablets came into contact with the dissolution medium, which was no doubt verified by investigations of DSC and analysis and IR analysis. Additionally, pH and the ionic strength of the dissolution medium were also found to exert an influence on the drug-release performance of SAL tablets, which may have a potential impact on the *in vivo* performance variation of SAL matrices between subjects.

## Declaration of interest

The authors report no declarations of interest.

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