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RESEARCH PAPER

The Effect of Citric Acid Added to Hydroxypropyl Methylcellulose (HPMC) Matrix Tablets on the Release Profile of Vinpocetine

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ABSTRACT

Vinpocetine is a pH-dependent experimental drug with a short half-life. The sustained-release matrix tablets of vinpocetine were prepared by direct compression using hydroxypropyl methylcellulose (HPMC) and different amounts of citric acid to set up a system bringing about gradual release of this drug. In order to investigate the influence of citric acid and the pH value of medium on the drug release from HPMC matrix tablets, an in vitro release test was carried out in either phosphate buffer pH 6.8 [0.5% sodium dodecyl sulfate (SDS)] for 12 hr or in 0.1 N HCl (0.5% SDS) (0–2 hr) and phosphate buffer pH 6.8 (0.5% SDS) (2–12 hr).Dissolution curves were described by the Peppas equation: $M_t/M_{inf}=kt^n$, and the influence of citric acid on the dissolution mechanism was estimated according to the regression parameter—n and k values. The addition of citric acid and the pH value of medium could notably influence the dissolution behavior and mechanism of drug-release from matrices. Increasing the amounts of citric acid produced an increase in drug release rate, which showed a good linear relationship between contents of citric acid and drug accumulate release (%) in phosphate buffer pH 6.8 (0.5% SDS) ($r>0.99$). Moreover, a higher drug release rate could be found in 0.1 N HCl (0.5% SDS) than that in phosphate buffer pH 6.8 (0.5% SDS) during the first two hours when the content of citric acid added to matrices was lower than 45 mg/tab., but no significant difference could be found when the content of citric acid was above that value. Increasing amounts of citric acid produced decreasing values of n and increasing values of k, in a linear relationship, which indicated there was a trend favoring the mechanism of diffusion with the addition of increasing quantities of citric acid.

Key Words: Vinpocetine; Release mechanism; Hydroxmethyl cellulose (HPMC); Citric acid; Sustained release; pH effect.

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INTRODUCTION

Vinpocetine was introduced in clinical practice in Hungary some 20 years ago for the treatment of cognitive disorders and related symptoms. Since then, its active ingredient, vinpocetine, besides its therapeutical utilization, has become a reference compound in the pharmacological research on 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, constant searches are needed not only for new and more powerful drugs, but also for more effective formulations of already known drugs. Because of short half-life of 2–4 hrs,[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 can not only significantly improve patient compliance, especially in case of chronic drug use, but they also reduce the total dosage of administered drug and, consequently, the possible side effects.

Hydrophilic polymer matrix systems are widely used in oral controlled-drug delivery because of flexibility in obtaining a desirable drug-release profile, cost effectiveness, and a broad U.S.Food and Drug Administration acceptance.[4] Hydroxypropyl methylcellulose (HPMC) is the dominant hydrophilic polymer carrier used for this kind of system.[5] Various investigators have studied many factors identified as modifiers of drug release, including drug loading,[8–10] drug:polymer ratio,[7–12] drug particle size,[8–10,13] HPMC particle size,[13,14] HPMC viscosity grade,[8,9] type of excipients, and manufacturing process.[15] Additionally, the aqueous solubility of the drug is also a main consideration in the design of a hydrophilic polymer matrix system. The release of drug considered to be a weak base or a weak acid could be markedly affected by the changing pH in the gastrointestinal tract. As to the weak basic drugs, a conversion of the more ionizable drug to a less soluble base may be caused by the penetration of intestinal juices with pH higher than that in the stomach. This conversion, total or partial, brings down the solubility and, therefore, the diffusion rate of the drug through the matrix. This effect is dependent of the pK_a of the drug and the pH of the intestinal fluids. The addition of some organic acids to matrix tablets has been used to improve the release rate of drugs insoluble in neuter or basic medium from hydrophilic matrices. Pelanserin hydrochloride release from HPMC matrix tablets was enhanced by adding citric acid to the formulations.[16] The release of papaverine·HCl in buffer pH 7.4 was improved by the incorporation of organic acids.[17]

Vinpocetine is a weak basic drug with distinct pH-dependent solubility. In order to improve its solubility in intestinal fluids, citric acid was added to HPMC matrices. The objective of the study described in this paper was to evaluate, systematically and quantitatively, the influence of admixed citric acid, a hydrosoluble acidic excipient, on the vinpocetine-release behavior and release mechanisms from HPMC (K4M) matrices in 0.1 N HCl (0.5% SDS) or in phosphate buffer pH 6.8 (0.5% SDS) medium.

Table 1. The compositions of different HPMC matrices containing citric acid or lactose.

Formula	Vinpocetine (mg)	K4M (mg)	Citric acid (mg)	Lactose (mg)	PH101 (mg)	Mg stearate (mg)
K1	15	75	—	—	110	2
K2	15	75	1	—	109	2
K3	15	75	3	—	107	2
K4	15	75	5	—	105	2
K4′	15	75	—	5	105	2
K5	15	75	10	—	100	2
K6	15	75	15	—	95	2
K7	15	75	30	—	80	2
K8	15	75	45	—	65	2
K8′	15	75	—	45	65	2
K9	15	75	60	—	50	2
K10	15	75	75	—	35	2
K11	15	75	90	—	20	2
K12	15	75	105	—	5	2
K12′	15	75	—	105	5	2

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MATERIALS AND METHODS

Materials

Vinpocetine was a gift from East–North Pharmaceutical Company (Shenyang, China). Hydroxypropyl methylcellulose (HPMC, K4M) was a gift from Colorcon Co. (UK). Microcrystalline cellulose, Avicel PH-101, was a gift from FMC Corporation, Philadelphia, Pennsylvania. 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.

Preparation of Compressed Matrices

Hydroxypropyl methylcellulose was used to produce matrices containing 15 mg vinpocetine with different ratios of vinpocetine:citric acid. In order to compare the effects of substituting lactose for citric acid on drug release, the same contents of lactose were added to matrices instead of citric acid in three formulas. The compositions of different tablet formulations are shown in Table 1. The drug and the cor responding quantities of the other components (HPMC K4M, citric acid or lactose, PH 101, and magnesium stearate) were completely mixed manually and then passed through an 80-mesh sieve 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, China) using a 7-mm flat-faced punch. Tablets with hardness values of 6∼8 kg were prepared by applying suitable compression forces. The tablet weight was 202 mg ± 5%.

In Vitro Release Tests

In vitro release tests were carried out using USP paddle (apparatus II) method an using ZRS-8G Intelligent Dissolution Tester (Tianjin University Radio Factory, Tianjin, China) at a speed of 50 rpm. 500 mL of 0.1 N HCl or phosphate buffer pH 6.8 containing 0.5% SDS at 37 ± 0.1°C was used as dissolution medium. Six sinkers were used in order to reduce the variability due to hydrodynamics conditions of the test and to overcome the problem due to possible sticking of the gelled matrix on the wall of the dissolution container. Filtered samples (5.0 mL) were withdrawn at predetermined time intervals and analyzed using an ultraviolet spectrophotometer (UV) at a wavelength of 268 nm (UV Spectrophotometer, Model UV-9100, Beijing Ruili Analysis Instrument Co. Beijing, China).

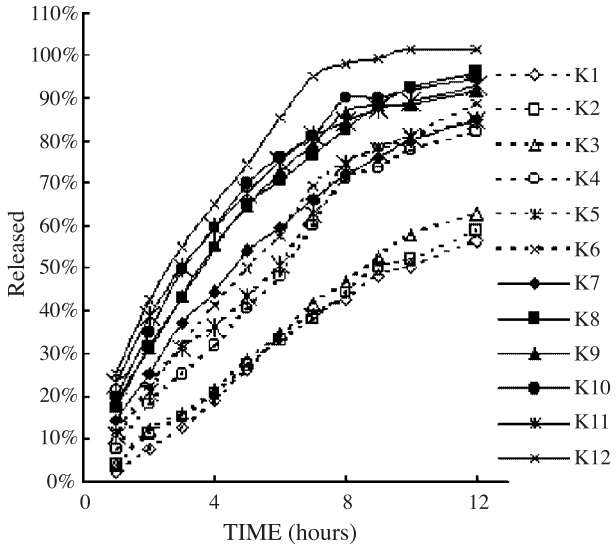

Figure 1. Dissolution of vinpocetine from HPMC matrices containing different amounts of citric acid, using phosphate buffer pH 6.8 (0.5% SDS) as medium. Averages of three repetitions.

Dissolution medium (5.0 mL) was added to maintain a constant volume. All release tests were run in triplicate, and mean values were reported (SD within about 4%).

Model Used for the Analysis of Drug Release Kinetics

The release data were fitted using the well-known empirical equation proposed by Korsmeyer and Peppas:[18,19]

$$M_t/M_{\text{inf}} = kt^n \quad (1)$$

Where M_t/M_{inf} is the accumulative release percent at time t, k is the kinetic constant incorporating structural and geometric characteristics of the release device, and n is the diffusional exponent indicative of the mechanism of drug release. The value of n for a cylinder is <0.45 for Fickian release, >0.45 and <0.89 for non-Fickian release, 0.89 for the case II release and >0.89 for the super case II type release.[20]

RESULTS AND DISCUSSION

Influence of Citric Acid Amounts on the Release Behavior of Drug from Matrices

A comparison of the release profiles of matrices containing different amounts of citric acid are shown in

Fig. 1. The amounts of citric acid is in the range of 0 to 105 mg/tab., while keeping the drug and polymer content constant, significantly affected the dissolution process in phosphate buffer pH 6.8 (0.5% SDS).

Generally, increasing the amounts of citric acid produced an increasing release rate of drug. Compared to the formula K1 containing no citric acid, only small amounts of citric acid (5 mg/tab., K4) present in combination with vinpocetine led to a notable increase of drug release rate and more complete drug release at the end of the dissolution period. It indicated the release behavior of vinpocetine was sensitive to the addition of citric acid. At 2 hr the amounts of drug dissolved increased from 7.64% (K1) to 18.12% (K4) and after 12 hr from 56.36% (K1) to 81.85% (K4).

From Fig. 2, it can be seen that the influence of citric acid on the release of vinpocetine existed at the first period (2 hr), middle period (5 hr) and latter period (8 hr). It indicated an early beginning of citric acid release that increased the dissolution rates from the first and along the whole process, but the effect level of citric acid was different in magnitude.

Additionally, release data of vinpocetine from matrices showed a good linear relationship to the amount of citric acid added to the HPMC matrices, especially during the first 2 hr, when the correlation coefficient was >0.99 as shown in Table 2. However, the value of R^2 became lower at 5 hr (0.9615) and 8 hr (0.8771). These results might be related to the dissolve and the sustained-release of citric acid out of the matrices. Due to its constant release from matrices, smaller amounts of citric acid would be present in the matrices, which reduced the citric acid effect in magnitude and, consequently, decreased the release rates of drug at middle and latter periods.

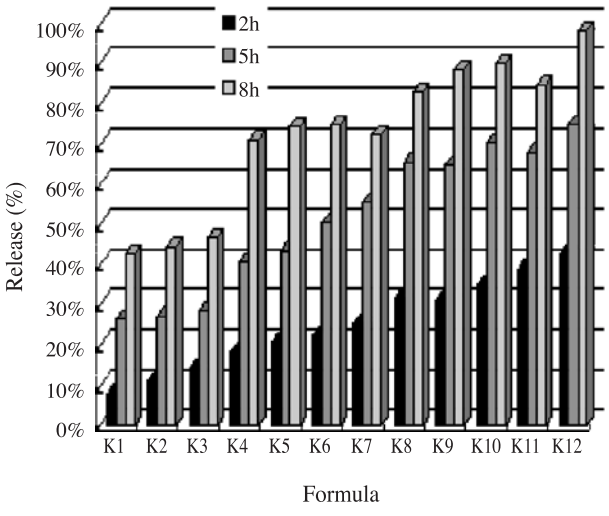

Figure 2. Dissolution of vinpocetine from HPMC matrices containing different amounts of citric acid at 2 hr, 5 hr, and 8 hr, using phosphate buffer pH 6.8 (0.5% SDS) as medium. Averages of three repetitions.

Table 2. Regression equation of vinpocetine dissolution curves from HPMC matrices containing different amounts of citric acid at 2 hr, 5 hr, and 8 hr.

T	Regression equation: $M_t = a\text{Citr.Ac.} + b$	R^2
2 hr	$M_{2h} = 0.0308$ Citr.Ac. $+ 0.0488$	0.9921
5 hr	$M_{5h} = 0.0482$ Citr.Ac. $+ 0.1981$	0.9615
8 hr	$M_{8h} = 0.0483$ Citr.Ac. $+ 0.4104$	0.8771

Influence of Citric Acid Amounts on the Release Mechanism of Drug from Matrices

Release data of vinpocetine from matrices containing various citric acid concentrations produced straight-line plots with Eq. 1 when the regressions were calculated for drug release in a time up to 10 hr. The correlation coefficients for most of data were >0.99 and other regression parameters for all curves in phosphate buffer pH 6.8 (0.5% SDS) are given in Table 3. Because of the phenomena of lag time, the values of exponent n for formulas K1, K2, and K3 were over 1. Linear trend could be found between the slope (n) of release curves and the citric acid content as well as between the release constant (k) and the citric acid content (Fig. 3). Increasing the amounts of citric acid produced decreasing values of n from 1.381 (K1) to 0.613 (K12), while increasing values of k from 0.027 (K1) to 0.263 (K12). These results indicated matrices processing a greater proportion of citric acid exhibited a drug release closer to a diffusion-controlled process and could release a higher amount of drug.

Theoretically, two concepts could contribute to the produced effects of citric acid on the drug release from HPMC matrices:

In the first aspect, citric acid could maintain a low pH inside the matrix and act in compensating for a decrease in solubility of vinpocetine in pH 6.8 medium. As a weak basic drug, the solubility of vinpocetine in phosphate buffer pH 6.8 was found to be much lower, (11.93±3.82) μg/mL, than that in 0.1 N HCl, (3938.67±241.89) μg/mL. At high pH, bases were always unionized and their solubility would be much lower. As the pH was gradually lowered, increasingly more base would be protonated and the solubility would begin to rise. The possibility of enhanced

Table 3. Regression parameters of vinpocetine curves from HPMC matrices, using phosphate buffer pH 6.8 (0.5% SDS) as medium, covering the time up to 10 hr.

Formula	Citric acid (mg)	Slope (n)	Intercept	R^2	k
K1	0	1.381	−3.612	0.986	0.027
K2	1	1.101	−3.105	0.993	0.045
K3	3	1.116	−3.068	0.991	0.047
K4	5	1.011	−2.514	0.994	0.081
K5	10	0.878	−2.197	0.995	0.111
K6	15	0.856	−2.093	0.995	0.123
K7	30	0.750	−1.880	0.993	0.153
K8	45	0.725	−1.674	0.995	0.187
K9	60	0.711	−1.642	0.986	0.194
K10	75	0.627	−1.434	0.991	0.238
K11	90	0.590	−1.385	0.989	0.250
K12	105	0.613	−1.337	0.995	0.263

dissolution of vinpocetine in a low pH circumstance was derived from an equation that follows the degree of ionization as described by the Henderson–Hasselbalch equation:[21]

$$C_s = C_{OB}(1 + 10^{pK_a - pH}) \quad (2)$$

C_s is the observed solubility at the given pH, and C_{OB} is the intrinsic solubility of the base. As reported, the pH of a 0.1N aqueous solution of citric acid is 2.2,[22] which is about 5 pH units lower than pK_a value (7.1) of vinpocetine.[23] So it could be considered that the drug would be mostly protonated and ionized in a relative low pH environment caused by the dissolution of citric acid when matrices came into solvent, independently of the pH of the biological fluids. In this manner, citric acid could increase the solubility as well as diffusion coefficient of vinpocetine, allowing a faster release of drug out of gel barrier around the matrices.

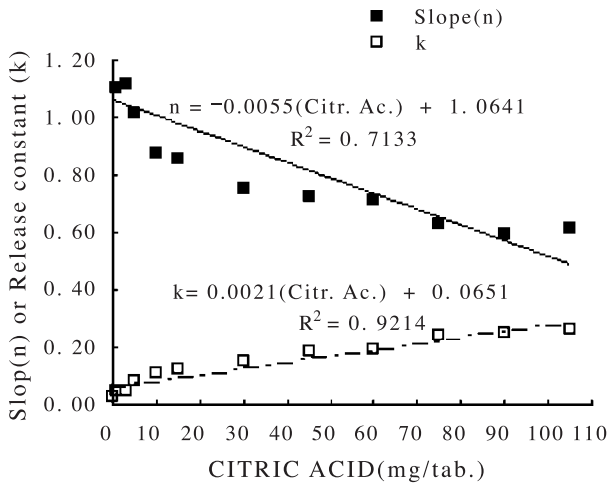

Figure 3. Relationship between the regression slope (n) and the release constant (k) of vinpocetine dissolution curves from HPMC matrices and their citric acid content (phosphate buffer pH6.8 (0.5% SDS) as medium for 0–10 hr).

In a second aspect, citric acid might loosen the matrix structure through an increased porosity created after its dissolution and release. It can be considered that swellable systems, like those made of HPMC particles, are based on polymers, which are controlled predominantly by the pore network rather than the polymer.[24] Citric acid is a high water soluble material, circa 67% w/w[22] or 210% w/v[25] at 37°C. During the in vitro dissolution test, the porosity and the thickness of depletion zone became greater after citric acid was lost from matrices gradually, which consequently induced the drug to diffuse from the matrix more easily.

In order to decide whether porosity played a major role in increasing drug release rate, the influences of lactose (another hydrosoluble excipient) on the vinpocetine release were compared to that of citric acid at low (5 mg/tab.), middle (45 mg/tab.), and high (105 mg/tab.) content levels respectively. As can be observed in Fig. 4, the main citric acid effect cannot be well explained with the second aspect because a much lower and incomplete release was found in the three formulas containing lactose compared to those containing the same contents of citric acid. This conclusion was different from that reported by Rogelio et al.,[16] in which the increasing porosity generated by dissolution of citric acid seemed the main contributor to the faster drug-release rate. Although the effect of adding lactose to hydrophilic matrices has been claimed to bring about marked increases in the

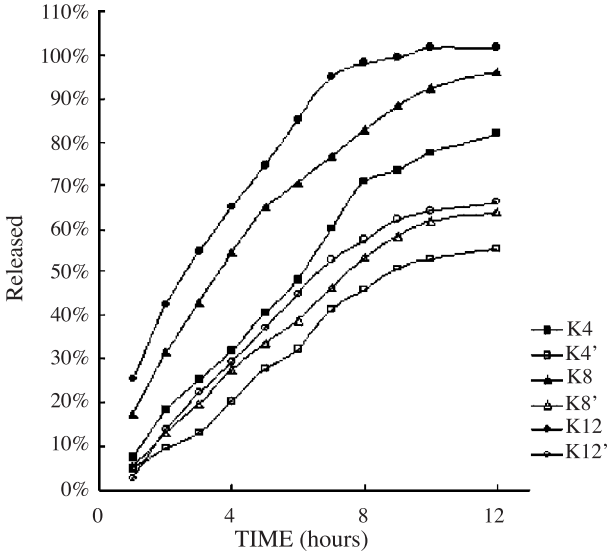

Figure 4. Comparison of lactose and citric acid on the vinpocetine release from HPMC matrices at three content levels, using phosphate buffer pH 6.8 (0.5% SDS) as medium. Averages of three repetitions.

release rate of hydrosoluble active principles by increasing the porosity and tortuosity of the pores and channels network,[26] it seemed not to be the case of the poorly soluble drug.[27] From the results of our investigation, increasing the amount of lactose brought about less significant increases of vinpocetine release from matrices. At the end of dissolution period, the drug release rate became much lower and the drug accumulate release percent nearly closed to a constant value (<70%), which indicated an incomplete release of vinpocetine would take place if it contained no citric acid, no matter how much lactose was added to HPMC matrices. Moreover, in contrast with Rogelio's work, direct compression was used in our study to prepare matrix tablets, which avoided dissolving the citric acid in a granulation process with water, as well as the ''separation of HPMC particles'' effect caused by the dissolution of citric acid deposited around HPMC.[16] Therefore, it could be concluded that the effect of citric acid seemed more the effect of an acidic than a hydrosoluble excipient. Maintenance of a low pH inside the matrix microenvironment would be the primary explanation for the higher and more complete drug dissolution in pH 6.8 medium when the citric acid contents increase. Matrices with high citric acid content would induce more ionized drug with high solubility to freely diffuse out of the gel surrounded by the surface of tablets, therefore, a larger dependence of the drug released mechanistically on drug diffusion. Matrices with solubility restrictions, like those with lower citric acid concentration, exhibit a shift towards drug release by relaxation mechanism.

Influence of Dissolution Media on the Release of Drug From Matrices

In order to investigate the effect of pH value of medium on the drug release from matrices, 0.1 N HCl (0.5% SDS) was used in in vitro release tests for the first 2 hr, simulating the gastric environment of human beings, and changed to phosphate buffer pH 6.8 (0.5% SDS) for the following 10 hr.

As Fig. 5 shows, increasing the amount of citric acid also produced an increase of the drug-release rate, similar to the results observed in single medium (phosphate buffer pH 6.8). However, there were more drugs released in 0.1 N HCl than in phosphate buffer pH 6.8 during the first two hours when citric acid content was lower than 45 mg/tab. (K1–K5) (data not listed in this paper), and there was a clear decrease in vinpocetine release rate when the pH of the medium was changed from 0.1 N HCl to pH 6.8. This was supposed to be due to the difference in the solubility of vinpocetine in acid medium and in neutral medium (see Table 4). When the amount of citric acid was low, the early dissolution of citric acid would be quick and

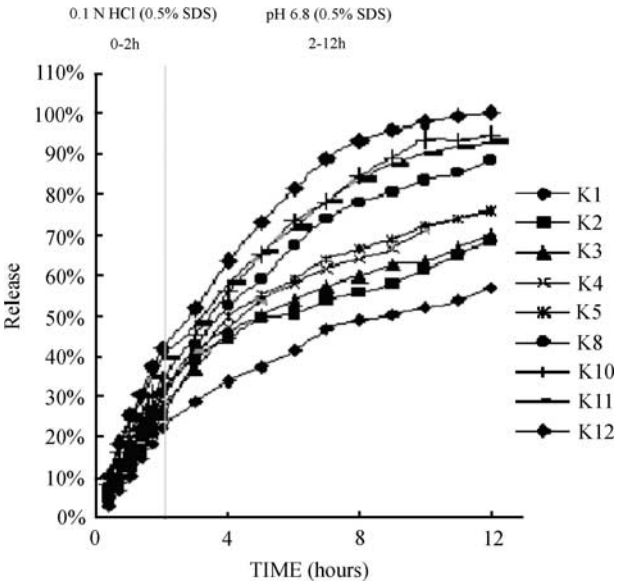

Figure 5. Dissolution of vinpocetine from HPMC matrices containing different amounts of citric acid, using 0.1N HCl (0.5% SDS) (0–2 hr) and phosphate buffer pH6.8 (0.5% SDS) (2–12 hr) as medium. Averages of three repetitions.

Table 4. Regression parameters of the vinpocetine dissolution curves from HPMC matrices, in the first part (0–2 hr) using 0.1 N HCl (0.5% SDS) as medium and in the second part (2–10 hr) using phosphate buffer pH 6.8 (0.5% SDS) as medium.

		0–2 hr			2–10 hr		
Formula	Citric acid (mg)	Slope (n)	k	R^2	Slope (n)	k	R^2
K1	0	1.092	0.105	0.999	0.568	0.152	0.993
K2	1	0.935	0.129	0.991	0.531	0.197	0.984
K3	3	0.830	0.158	0.998	0.55	0.199	0.991
K4	5	0.855	0.166	1.000	0.539	0.218	0.994
K5	10	0.812	0.185	0.997	0.536	0.226	0.991
K8	45	0.807	0.176	0.998	0.517	0.256	0.996
K10	75	0.794	0.206	0.993	0.506	0.264	0.999
K11	90	0.765	0.237	0.998	0.497	0.287	0.991
K12	105	0.778	0.249	0.999	0.507	0.310	0.994

complete before the change in pH occurred. It couldn't compensate for the reduction of solubility in pH 6.8, in spite of the possible contribution to pH of citric acid. The effect of this change in solubility, therefore, decreased diffusion of vinpocetine through the gel barrier.However, in contrast, when the amount of citric acid was higher than 45 mg/tab. (K8, K10–12), the citric acid produced a similar release rate of vinpocetine in both mediums. In this case, the early dissolution of citric acid might be slower and incomplete, consequently, the remaining amount of citric acid could be enough to act to recovering a drop in solubility after changing the pH through increasing the release rate of vinpocetine in phosphate buffer pH 6.8 as well as improving the degree of curvature of the entire release profiles. These results also indicated a pH-independent release profile could be obtained for a weak basic drug by adding appropriate amount of citric acid to HPMC matrices.

Because of the slowing down of drug release cause by the change or adjustment after 2 hr, the curvature of the drug-release profile appeared different in 0.1 N HCl and pH 6.8 for some formulas. Therefore, a better fit to Eq. (1) could be obtained by calculating the regression divided into two parts, for the release profile in 0.1 N HCl (0–2 hr) and for the release profile in phosphate buffer pH 6.8 (2–10 hr). The regression parameters for all curves were given in Table 4, in which it can be seen that the correlation coefficients for most of the data were >0.99 and the slopes or n values calculated for vinpocetine in 0.1 N HCl were between 0.778 for K12 and 1.092 for K1 and in pH 6.8 were 0.507 and 0.568 (Table 4). These data indicated that the drug release mechanism might be attributed to a non-Fickian release process for all the cases, as would be expected for swellable matrices.

There was a liner trend to decreasing values of the exponent n as the matrices' citric acid content increased (Fig. 6). Similarly, matrices possessing greater proportions of citric acid exhibited a drug release closer to a diffusion-controlled process. These effects could be well explained by the first aspect of citric acid effect discussed. Moreover, the average slope (n) of the release process of matrices in pH 6.8 for 2∼10 hr calculated from data given in Table 4 (0.528) showed a lower value than that calculated from

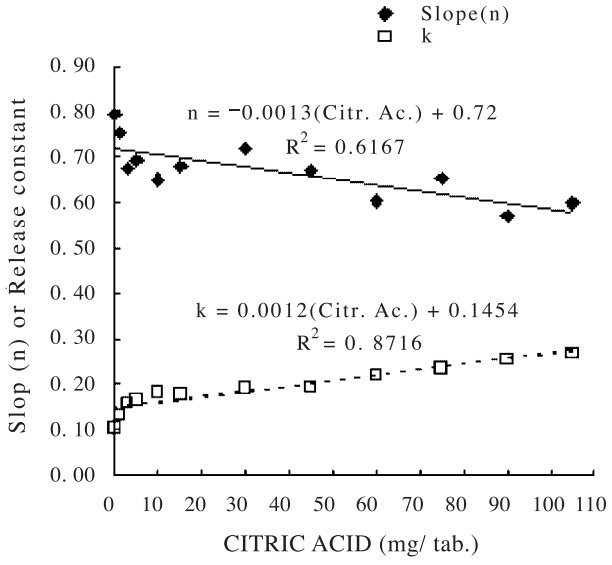

Figure 6. Relationship between the regression slope (n) or the release constant (k) of vinpocetine dissolution curves from HPMC matrices and their citric acid content (0.1 N HCl (0.5% SDS) (0–2 hr) and phosphate buffer pH6.8 (0.5% SDS) (2–12 hr) as medium.

data given in Table 3 (0.894). This suggested a greater dependence of matrices on the mechanism of diffusion for the drug release in changing dissolution medium. The maintenance of an acid medium in the matrices compensated for the decrease of solubility after changing the pH and increased the diffusion coefficient of vinpocetine out of matrices, consequently, making the dissolution process more dependent on the mechanism of diffusion.

CONCLUSION

Vinpocetine matrices were successfully prepared by direct compression using HPMC K4M with different amounts of citric acid added to the matrices, which made possible a sustained release of vinpocetine with a coupled dissolution mechanism of diffusion/relaxation. The drug release was markedly influenced by the amount of citric acid added to HPMC matrices and the pH value of medium using an in vitro dissolution test. The addition of citric acid to HPMC matrices produced greater dissolution rates dependent on citric acid content, which showed a good linear relationship between content of citric acid and drug accumulate release (%) in phosphate buffer pH 6.8 (0.5% SDS). More drugs could be released in 0.1 N HCl (0.5% SDS) than in phosphate buffer pH 6.8 (0.5% SDS) if the amount of citric acid was lower than 45 mg/tab., but no significant difference was found when amounts of citric acid were above that value. These effects were confirmed mainly due to the maintenance of a low pH microenvironment generated by the gradual dissolution and release of citric acid inside the matrix, which could compensate for a decrease in solubility after changing the pH 1.0 to 6.8. Mechanistically, there was a linear trend to increasing values of release constant k and to decreasing values of diffusion exponent n as the amount of citric acid added to matrices increased, which indicated there was a trend favoring the mechanism of diffusion with the addition of increasing quantities of citric acid.

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