Journal of Pharmaceutical and Biomedical Analysis 54 (2011) 711–716

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Evaluation of powder mixtures and hydrophilic gastroretentive drug delivery systems containing zinc acetate and sodium bicarbonate

Gabriella Baki, János Bajdik, Klára Pintye-Hódi*

Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary

ARTICLE INFO

Article history:
Received 28 July 2010
Received in revised form 13 October 2010
Accepted 29 October 2010
Available online 9 November 2010

Keywords:
Zinc acetate dihydrate
Sodium bicarbonate
Water uptake
Disintegration
Floating
Dissolution

ABSTRACT

The aim of this study was to develop and study floating controlled drug delivery systems consisting of a model drug (zinc acetate dihydrate), different forms of a matrix-forming polymer (Metolose 90 SH) and sodium bicarbonate as an effervescent component. The proportions of Metolose and bicarbonate were varied, and the effects of the different ratios on the properties of the resulting powders and tablets were determined. The water uptakes of different powder mixtures were initially evaluated. These tests indicated the interaction of the active and effervescent agent, this phenomenon leading to an unpredicted increase in the amount of liquid taken up. This interaction was evaluated as concerns the degradation of the hydrophilic matrix system. The disintegration of tablets with different compositions revealed that this interaction increases the time required for the disintegration of these systems. The study demonstrated that the interaction of the components induced significant changes in the parameters of this new sensitive delivery system. In the last steps, the buoyancy and dissolution properties of tablets that appeared appropriate for the formulation of a controlled drug delivery system were investigated.

1. Introduction

Zinc acetate has a wide range of medical and dietary applications, e.g. as a dietary supplement, as an adstringent [1] or in lozenges used to treat the common cold [2]. Zinc salts, e.g. the sulfate, gluconate or acetate, can also be used to treat zinc deficiencies. As an oral daily supplement, this metal ion is used for the treatment of Wilson disease, an inherited, copper accumulation disorder that affects about 30 individuals per million people [3]. It is due to a dysfunction of a copper-transporting ATPase [4,5], leading to an accumulation of copper, mainly in the liver, but also in the brain, cornea and kidney, and causing progressive hepatic and nervous system damage. In the treatment of this disease, different active agents and their combinations can be applied, depending on the severity of the symptoms [6]. Zinc was first used by Schouwink in The Netherlands in the early 1960s [7,8]. Zinc interferes with the uptake of copper from the gastrointestinal tract, and removes stored copper [9]. Zinc may also act by inducing elevated levels of metallothionein [10–12]. Dosing is in the order of milligrams of zinc: the necessary amount is 150 mg of zinc per day. Thus, zinc sulfate, for instance, should be administered in a dose of 220 mg/day three times daily [13]. The actual salt used does not make a difference with respect to efficacy, but may affect tolerability [14]. Acetate may cause the least gastrointestinal distress, and gluconate may be more tolerable than sulfate. In the case of active agents with a short elimination half-life in the plasma, administration two or three times a day is necessary, but the compliance and tolerability of patients can be increased by developing a sustained-release system.

The primary site of absorption of exogenous zinc in the human is thought to be in the proximal small bowel [15,16]. In order to develop a desired sustained-release dosage form for zinc acetate, it is necessary to optimize both the residence time of the system in the gastrointestinal (GI) tract and the rate of release of the drug. Various approaches are used to increase the GI residence time, including mucoadhesive systems [17,18], swellable systems [19] and flotation systems [20,21]. Floating drug delivery systems (FDDSs) remain buoyant in the stomach for a prolonged period of time because of their lower bulk density as compared with that of the aqueous medium. These systems can involve the use of carbonates and bicarbonates, for example [22–24]; when these come into contact with acidic aqueous media, carbon dioxide is generated and entrapped within the gelling hydrocolloid, causing the system to float. An FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine [25]. These systems help in releasing the active agent continuously before it reaches the absorption window, thereby ensuring optimum bioavailability [26].

In our work, hydrophilic floating matrix tablets were prepared by direct compression. Compressed hydrophilic matrix tablets are

* Corresponding author. Tel.: +36 62 545 576; fax: +36 62 545 571.
E-mail address: klara.hodi@pharm.u-szeged.hu (K. Pintye-Hódi).

0731-7085/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2010.10.026

commonly used as oral drug delivery systems because of their good compactibility. Drug release from these systems is controlled by the formation of a viscous layer around the tablet, which acts as a barrier by opposing the penetration of water into the tablet. The overall drug release is influenced not only by the drug solubility, but also by the physical and mechanical properties of the gel barrier. Besides the mechanism of drug release, the extents of matrix swelling and erosion, and the diffusion of the drug determine the kinetics [27].

For FDDSs, rapid hydration is a basic requirement. It is well known from the literature that Metolose matrices hydrate rapidly only at the surface [28], retaining the bubbles developing from sodium bicarbonate and extending flotation during 8 h. The addition of sodium bicarbonate expands the volume of the matrices due to the gas bubbles formed after reaction with the acidic dissolution medium [29] and with the active agent, increasing their hydration volume.

In this study, a new FDDS based on the gas formation technique was developed. The tablets were prepared by direct compression, containing different ratios of an effervescent component (sodium bicarbonate) and different types of hydroxypropyl methylcellulose as matrix former. Zinc acetate dihydrate (Zn-ac), which is predominantly absorbed in the upper part of the GI tract, was used as active compound. It is known that interaction may occur between bicarbonates and Zn-ac [30]; accordingly, the objective of this work was to prepare a controlled drug delivery system and to investigate the effects of the ingredients and their possible interaction on the properties of powder mixtures (water uptake) and tablets (disintegration, floating and dissolution). In this part of our work, only the technological aspects were studied. The chemical relevance and the background will be discussed later. Our aim was an evaluation of the effects of the components on the functioning and erosion of this hydrophilic floating system.

2. Materials and methods

2.1. Materials

Zn-acetate (Zn-ac) (Merck KGaA, Darmstadt, Germany) was chosen as active agent. Forms of hydroxypropyl methylcellulose (Metolose 90 SH 100 SR, 4000 SR, 100,000 SR, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) with different viscosities were used as matrix-former. This component is frequently utilized to form floating matrix systems [24,31]. The notations for the different (low, medium and high) viscosities of the Metolose used in this work were as the follows: 100 SR – LV, 4000 SR – MV and 100,000 SR – HV. Sodium bicarbonate ($NaHCO_3$, Solvay S.A., Brussels, Belgium) was applied as gas-forming agent. Lactose monohydrate (Ph. Eur., Hungaropharma Plc, Budapest, Hungary) was used to substitute Zn-ac in the second part of the work.

2.2. Preparation of powder mixtures

As a preliminary step, the Zn-ac and $NaHCO_3$ were size-reduced in a mortar (Retsch RM 100, Retsch GmbH, Haan) for 10 min. Particle sizes were determined with an analytical sieve (Retsch GmbH, Haan) and particles with diameters of 100–200 μm were used in the study. The drug and the excipients were mixed in a rotating shaker mixer (Turbula, Willy A. Bachofen Maschinenfabrik, Basel) at 50 rpm for 10 min. The amount of active agent was calculated on the basis of the zinc requirement, which is equivalent to 500 mg of Zn-ac a day. The mass of the tablets prepared was 1 g. Powder mixtures in every case contained 50% Zn-ac, while the ratio of $NaHCO_3$ and Metolose was varied as follows: 10:40%, 15:35%, 20:30% and 25:25% (w/w).

2.3. Evaluation of water uptake

The Enslin number, a simple semiquantitative measure of the water uptake of a powder, is the amount of fluid absorbed by 1 g of the powder (in ml/g). An Enslin apparatus with a glass filter and a pipette with 0.01 ml accuracy were used for these experiments [32]. 0.1 g of the different forms of Metolose, 0.25 g of each powder mixture and 0.5 g each of Zn-ac and $NaHCO_3$ were tested; 5 parallel experiments were performed in every case.

2.4. Preparation of matrix tablets

Tablets were prepared with a hydraulic press (Specac Inc., Graseby, England); round and flat punches 13 mm in diameter were used. 1 g of powder mixture was compressed at 3×10^8 Pa with a dwell time of 10 s. Additional excipients (lubricant and glidant) were not applied. In the second part of the work, powder mixtures containing lactose monohydrate instead of Zn-ac were prepared; the ratio of the components was not changed.

2.5. Study of matrix disintegration

The disintegration of tablets was evaluated with a disintegration tester (Erweka ZT 71, Erweka GmbH, Heusenstamm, Germany), tablets were stored in a desiccator for 24 h before the test. The test liquid was gastric fluid (pH 1.2, Ph. Eur.) and the temperature was 37 °C. Twelve parallel experiments were performed. Each test was carried out for a maximum of 8 h, as floating systems with a residence time in the stomach longer than 8 h are not reasonable [33].

2.6. Buoyancy

The buoyancy of the tablets was studied at 37 ± 0.5 °C, in 150 ml of gastric fluid at pH 1.2 (Ph. Eur.). The floating lag times (the duration of the period between the placing of the tablet in the medium and the tablet floating) and durations of tablet floating were determined by visual observation. Tablets were stored in a desiccator for 24 h before the test.

2.7. Dissolution study

The rates of *in vitro* release of Zn-ac from the matrix tablets were determined in 900 ml gastric acid (pH 1.2, Ph. Eur.) by the paddle method (Ph. Eur.). Tablets were stored in a desiccator for 24 h before the test. The paddle rotation speed was kept at 50 rpm, and the temperature at 37 ± 0.5 °C. Dissolution tests were carried out under sink conditions. The motor activity of the stomach in the fed state is induced 5–10 min after the ingestion of a meal; the larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2–6 h, or more typically, 3–4 h. The phasic contractions are similar to those seen during phase 2 of the interdigestive myoelectric motor complex (IMMC) in the fasting state [34]. Thus, the dissolution study was carried out for 4 h. Three millilitre samples were withdrawn at 0.5, 1, 1.5, 2, 3 and 4 h, and the Zn contents were measured by X-ray fluoresence analysis (Philips MiniPal PW 4025, Philips Analytical, Almelo, The Netherlands). During the measurements, the conditions applied were 12 kV and 100 μA, with a kapton filter and an air purge. The samples were measured during 60 s, repeated in triplicate for each sample.

The concentrations of zinc (ppm) were calculated by means of linear calibration ($r^2 = 0.9945$) from the intensities of the K_α lines of the detected radiation. The dissolved drug concentration was calculated on the basis of the zinc content of Zn-ac.

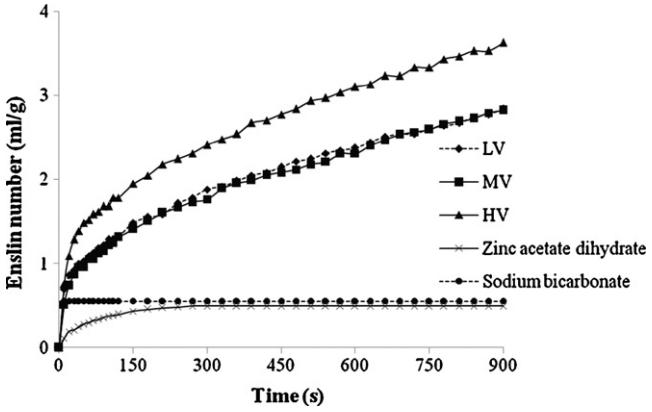

Fig. 1. Enslin numbers of active agent and excipients.

3. Results and discussion

3.1. Water uptake of different powder mixtures

For an understanding of the effects of the individual components on the water uptake of the system, the components and the binary and ternary powder mixtures were tested before the evaluation of the tablets. A requirement for floatable systems is that they should take up sufficient water to be able to enclose the developing air bubbles during the initial period of wetting. Thus, water uptake measurements were carried out for 15 min.

First, the Enslin numbers of Zn-ac and the excipients were determined (Fig. 1). The water uptakes of the different forms of Metolose were prolonged: for the LV and MV samples, the values were almost the same (LV: 2.838 ± 0.055 ml/g and MV: 2.819 ± 0.185 ml/g), whereas the quantity of water was higher for the HV sample (3.629 ± 0.161 ml/g). Their wetting was not finished by the end of the test. This was caused by the restriction of the gel layer of the swelling polymer. The process was very short in the case of $NaHCO_3$; the water uptake occurred in the first 10 s, after which the value was constant (0.553 ± 0.023 ml/g). The active agent took up the maximum quantity of water in the first 6 min, after which the value was constant (0.493 ± 0.031 ml/g) (Fig. 1).

Next, the water uptakes of the different binary and ternary powder mixtures were determined. The theoretical Enslin numbers were calculated from the Enslin numbers of each component in the ratio of their presence in the powder mixtures. Deviations from the calculated values were also determined. If a powder mixture took up the calculated maximum amount of water, there was no deviation, which meant a value of 100%.

First, the water uptakes of the ternary powder mixtures were determined (Table 1). The quantity of water taken up increased with increasing amount of $NaHCO_3$ in all cases. This change was unexpected as the Metolose content decreased with increasing amount of $NaHCO_3$. It would appear obvious that $NaHCO_3$ formed bubbles, which weakened the gel layer formed and the powder mixtures, so that they could hydrate more quickly.

Deviations from the calculated Enslin numbers were determined. Powder mixtures with 10% $NaHCO_3$ could not take up the calculated amount of water, and thus this ratio of $NaHCO_3$ was not sufficient to modify the structures of the powders (Table 1). In contrast, all of the other powders took up much more water than expected (almost double the calculated value). This indicates that something happened when the powder mixture came into contact with water. $NaHCO_3$ can react with acidic salts [35] such as Zn-ac, and carbonate salts are presumed to develop during the measurements.

For the evaluation of this situation, the binary mixtures were tested. When there was no $NaHCO_3$ in the powder mixtures (Table 2), a lower quantity of water was taken up, confirming that $NaHCO_3$ is required to change the structures of the powder mixtures and the gel layer of the polymer, enhancing the water uptake. Zn-ac itself slowed down the water uptake and reduced the amount of water taken up.

For the binary powder mixtures containing only the additives, lower amounts of water were taken up as compared with the calculated values, clearly demonstrating that the active agent was also indispensable for the unpredicted wetting (Table 3). This phenomenon points to an interaction between $NaHCO_3$ and Zn-ac, which enhances the water-uptake property of the powders.

The properties of powder mixtures without Metolose were also studied. The Enslin numbers of the 50:10, 50:15, 50:20 and 50:25 mixtures of Zn-ac:$NaHCO_3$ were as follows: 0.666 ± 0.023 (132.32% deviation), 0.859 ± 0.020 (169.45% deviation), 1.079 ± 0.073 (211.43% deviation) and 1.099 ± 0.021 (214.18% deviation), respectively. These two components together (Zn-ac and $NaHCO_3$) were able to take up more water than expected, confirming the occurrence of an interaction. At 20% and 25% $NaHCO_3$ contents,

Table 1
Enslin numbers (ml/g) (means ± SD) and deviation from calculated Enslin numbers (%) of ternary powder mixtures.

Zn-ac:$NaHCO_3$:Metolose (%) (w/w/w)	LV		MV		HV	
	Enslin number (ml/g)	Deviation (%)	Enslin number (ml/g)	Deviation (%)	Enslin number (ml/g)	Deviation (%)
50:10:40	1.383 ± 0.061	96.22	1.237 ± 0.039	86.54	1.571 ± 0.023	89.60
50:15:35	1.462 ± 0.101	110.55	1.474 ± 0.119	111.98	1.756 ± 0.078	109.75
50:20:30	1,927 ± 0.059	159.44	1.781 ± 0.085	147.37	1.996 ± 0.185	138.04
50:25:25	2.361 ± 0.089	215.76	1.929 ± 0.104	176.26	2.379 ± 0.023	184.17

Table 2
Enslin numbers (ml/g) (means ± SD) and deviation from calculated Enslin numbers (%) of binary powder mixtures without sodium bicarbonate.

Zn-ac:$NaHCO_3$:Metolose (%) (w/w/w)	LV		MV		HV	
	Enslin number (ml/g)	Deviation (%)	Enslin number (ml/g)	Deviation (%)	Enslin number (ml/g)	Deviation (%)
50:0:40	1.090 ± 0.045	71.01	1.104 ± 0.048	72.31	1.182 ± 0.047	62.66
50:0:35	1.077 ± 0.071	73.87	1.103 ± 0.084	76.02	1.196 ± 0.040	66.70
50:0:30	0.985 ± 0.024	71.75	1.102 ± 0.083	80.71	1.264 ± 0.026	75.71
50:0:25	0.957 ± 0.001	75.07	1.102 ± 0.062	86.84	1.316 ± 0.118	85.56

Table 3
Enslin numbers (ml/g) (means ± SD) and deviation from calculated Enslin numbers (%) of binary powder mixtures without zinc acetate dihydrate.

Zn-ac:$NaHCO_3$:Metolose (%) (w/w/w)	LV		MV		HV	
	Enslin number (ml/g)	Deviation (%)	Enslin number (ml/g)	Deviation (%)	Enslin number (ml/g)	Deviation (%)
0:10:40	0.930 ± 0.084	39.08	1.091 ± 0.024	45.84	1.342 ± 0.025	56.37
015:35	0.930 ± 0.100	43.21	0.985 ± 0.121	45.76	1.332 ± 0.024	61.89
0:20:30	1.145 ± 0.022	59.49	1.090 ± 0.043	56.67	1.281 ± 0.106	66.56
0:25:25	1.184 ± 0.062	69.83	1.105 ± 0.062	65.15	1.372 ± 0.206	80.91

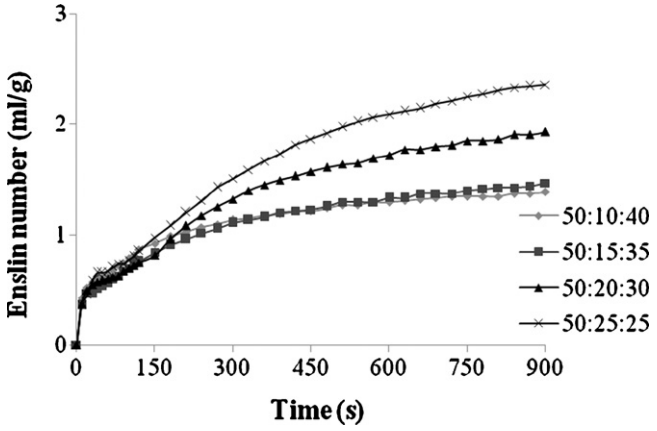

Fig. 2. Enslin numbers of ternary powder mixtures with LV. Zn-ac:$NaHCO_3$:Metolose ratios (w/w/w).

the amounts of water taken up were more than double. This interaction was also observed for the ternary powder mixtures, where higher amounts of water were taken up. The nature of this significant interaction which influenced the water-uptake properties of the powders appreciably must be studied in detail in the future.

$NaHCO_3$ influenced not only the extent of the water uptake of the powder mixtures, but also the kinetics of this process (Fig. 2). In the first 3 min, a step could be seen in all of the curves; this was most marked for the powder mixtures with LV.

3.2. Study of tablet disintegration

These tests were performed in consecutive steps. First, tablets prepared from the ternary powder mixtures were evaluated (Table 4). The tablets prepared from Metolose with different viscosities differed appreciably in behaviour. For LV, the time needed for disintegration of the tablets with the highest Metolose content was approximately 10 min, which was slightly more than for the other compositions. Thus, there was no prolonging effect in these tablets: only a few minutes was necessary for the complete disintegration of the systems.

At higher viscosities, unexpected behaviour of the tablets was experienced. At 10% $NaHCO_3$ content, a higher initial value was observed for both MV and HV Metolose, and thus the effect of the effervescent component in these mixtures was not significant. At higher $NaHCO_3$ content, there was a continuous increase in the duration of disintegration. For these tablets, the disintegration time did not decrease with increasing amount of $NaHCO_3$ as was expected on the basis of contact angle measurements, but continuously increased, so that there was a prolonged effect. The presumed interaction appeared to be proven, as the composition and consequently the properties of the powder mixtures changed on contact with water. The more significant the interaction was, the greater the extended behaviour of the system. It affected not only the water-uptake properties of the powder mixtures, but also the duration of disintegration.

To confirm this, other tests were performed. The duration of disintegration of the polymers and the binary powder mixtures containing Zn-ac and the different forms of Metolose were also measured, was and were more than 8 h in every case. Hence, it can be stated that the presence of $NaHCO_3$ is necessary for the detected disintegration time.

In the following step, the active agent, which is a necessary component of the interaction, was substituted with lactose monohydrate. The solubility of this component is similar to that of Zn-ac in water and there is no known interaction between lactose and the other components. The disintegration time of the tablets was then measured again (Table 5). A decrease in the erosion time of the tablets was detected with increasing content of $NaHCO_3$. This tendency was detected for every Metolose sample. In accordance with expectations, the binding effect of the smaller amount of polymer was insufficient to counteract the disintegration effect of the gas-forming component. These tests emphasized the importance of the interaction between the active and effervescent agent on the erosion of the dosage form.

3.3. Buoyancy of matrix tablets

The gastric floating system involved sodium bicarbonate as a gas-forming agent dispersed in the hydrogel matrix. On reacting with hydrochloric acid, the bicarbonate ion is converted to carbon dioxide in the form bubbles on the surface of the tablets, which caused the tablets to float in the fluid for more than 4 h *in vitro*. On the basis of the disintegration studies, it can be stated that only HV samples might be appropriate for the formulation of a floating drug delivery system. Thus, only these tablets were investigated further in this study; floating lag times and buoyancy (Fig. 3) were determined visually. The floating lag time for the samples containing 10% or 15% $NaHCO_3$ was shorter than 1 min, while for the samples with 20% or 25% gas-forming agent it was 4.1 ± 0.7 min and 3.5 ± 0.3 min,

Table 4
Disintegration times (min) of tablets prepared from ternary powder mixtures (means ± SD).

Zn-ac:$NaHCO_3$:Metolose (%) (w/w/w)	LV	MV	HV
50:10:40	10.5 ± 0.8	31.5 ± 13.9	>480.0
50:15:35	10.4 ± 1.2	15.2 ± 4.3	153.3 ± 37.0
50:20:30	10.2 ± 2.0	21.6 ± 6.0	231.2 ± 74.1
50:25:25	7.3 ± 1.0	80.2 ± 10.2	336.8 ± 58.6

Table 5
Disintegration times (min) of tablets prepared from powder mixtures containing lactose monohydrate (means ± SD).

Lactose:$NaHCO_3$:Metolose (%) (w/w/w)	LV	MV	HV
50:10:40	46.1 ± 9.1	>480.0	>480.0
50:15:35	23.8 ± 1.6	109.9 ± 13.5	>480.0
50:20:30	19.0 ± 1.1	62.8 ± 10.4	70.2 ± 16.6
50:25:25	14.3 ± 0.8	13.7 ± 1.2	20.4 ± 1.9

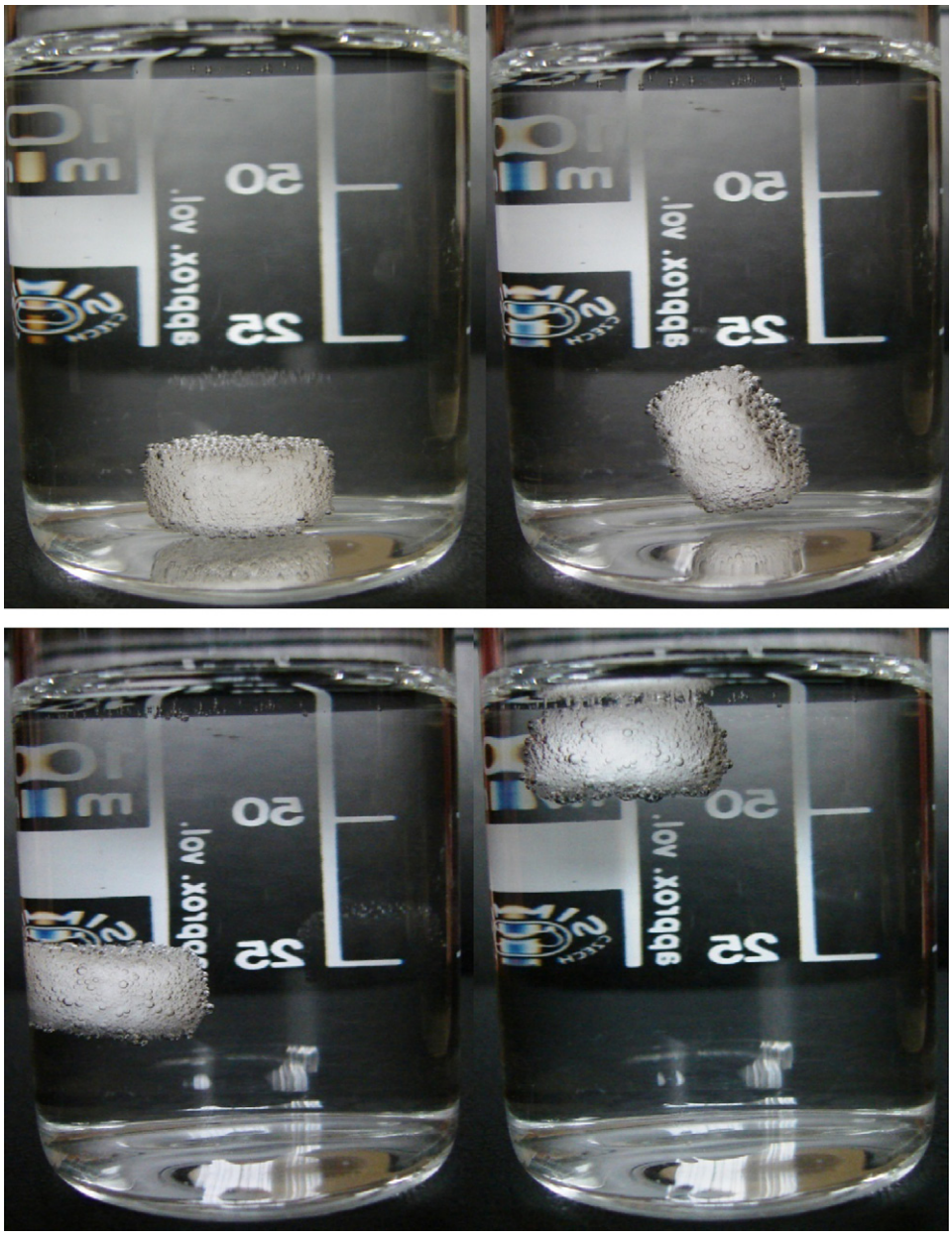

Fig. 3. Buoyancy of tablets (0–12 min).

respectively. The samples with 10% or 15% $NaHCO_3$ content floated for only 17 min and 64 min, respectively, which is not appropriate for the formulation of a floating system, whereas the samples with 20 or 25% gas-forming agent floated for a minimum of 4 h.

3.4. *In vitro dissolution study*

From the results of the preformulation studies of the initial twelve compositions, the HV mixtures with higher $NaHCO_3$ contents (20% and 25%) proved be appropriate for an extended release preparation. The dissolution characteristics of the sample with 20% gas-forming agent and 30% Metolose were studied (Fig. 4). It was obvious, that the bulk of the active agent dissolved in the initial period of time after coming into contact with the gastric acid, while the dissolution of the remaining part was slow and continuous. The initial fast dissolution may be explained by the fact that the buoyancy of the floating tablet in the stomach started 4 min after its reaction with the gastric acid; during this time, the evolving gas

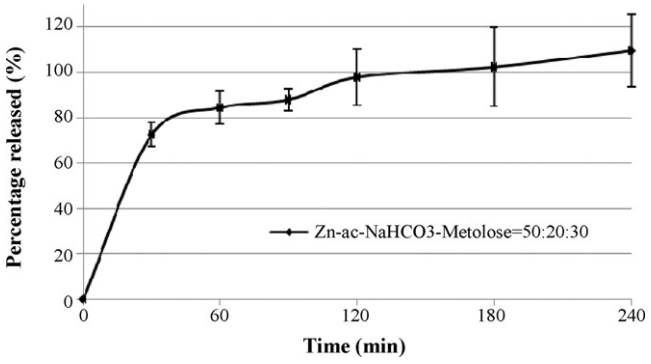

Fig. 4. Dissolution study.

permeated through the matrix leaving gas bubbles or pores which could have increased the rate of release of the active ingredient from the matrix. After that time, the gas bubbles were entrapped in the gel layer, which could have slowed down the dissolution.

4. Conclusions

Appropriate systems with prolonged disintegration times, appropriate buoyancy and controlled release can be formulated from Zn-ac by using $NaHCO_3$ as gas-forming agent and Metolose 90 SH 100,000 SR as a matrix and gel-forming component. In this case, the low viscosity grades of the polymer were not appropriate. Alteration of the ratio of the excipients resulted in an unpredicted significant influence on the properties of the dosage form. The interaction between Zn-ac and $NaHCO_3$ caused a relevant modification in the water uptake of the powder mixture and in the disintegration of the tablets. Independent tests revealed an interaction between these two components when they came into contact with water, so that prediction of the properties of the dosage form from the parameters of the starting components was impossible. This phenomenon was applied to develop a prolonged effect. Through investigation of the nature of this interaction, a better understanding of the process may be achieved. These technological aspects must therefore be studied with different chemical and biopharmaceutical tests. This is a good example of significant changes induced by interaction in the parameters of a new sensitive delivery system.

The floating study clarified what compositions may be suitable for the formulation of a controlled delivery system. The dissolution study demonstrated that the HV mixture with a higher $NaHCO_3$ content appeared appropriate for an extended release preparation, and this composition will therefore be investigated from a chemical aspect in the future. As the liberation of zinc in absorbable form can be achieved, it will be favourable if the interaction is controllable. These results may therefore be useful in the development from Zn-ac of a sustained release dosage form with a prolonged gastric residence time for the treatment of Wilson disease.

References

[1] A.F. Hefti, B. Huber, The effect on early plaque formation, gingivitis and salivary bacterial counts of mouthwashes containing hexetidine/zinc, amine-fluoride/tin or chlorhexidine, J. Clin. Periodontol. 14 (2005) 515–518.
[2] P. Little, Zinc acetate lozenges reduced the duration and severity of symptoms of the common cold, Evid. Based Med. 6 (2001) 46.
[3] M. Frydman, Genetic aspects of Wilson's disease, J. Gastroenterol. Hepatol. 5 (1990) 483–490.
[4] P.C. Bull, G.R. Thomas, J.M. Rommens, J.R. Forbes, D.W. Cox, The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene, Nat. Genet. 5 (1993) 327–337.
[5] R.E. Tanzi, K. Petrukhin, I. Chernov, J.L. Pellequer, W. Wasco, B. Ross, et al., The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene, Nat. Genet. 5 (1993) 344–350.
[6] J. Nagy, Z. Vincze, A. Folhoffer, A. Horváth, T. Csák, R. Zelkó, The pathomechanism and treatment of Wilson disease, Acta Pharm. Hung. 73 (2004) 237–241.
[7] T.U. Hoogenraad, J. Van Hattum, C.J. Van den Hamer, Management of Wilson's disease with zinc sulphate. Experience in a series of 27 patients, J. Neurol. Sci. 77 (1987) 137–146.
[8] T.U. Hoogenraad, R. Koevoet, E.G. de Ruyter Korver, Oral zinc sulphate as long-term treatment in Wilson's disease (hepatolenticular degeneration), Eur. Neurol. 18 (1979) 205–211.
[9] G.J. Brewer, R.D. Dick, V.D. Johnson, J.A. Brunberg, K.J. Kluin, J.K. Fink, Treatment of Wilson's disease with zinc. XV. Long-term follow-up studies, J. Lab. Clin. Med. 132 (1999) 264–278.
[10] M. Schilsky, R.R. Blank, M.J. Czaja, I.H. Scheinberg, R.J. Stockert, I. Sternlieb, Hepatocellular copper toxicity and its attenuation by zinc, J. Clin. Invest. 84 (1989) 1562–1568.
[11] G.M. Hill, G.J. Brewer, A.S. Prasad, C.R. Hydrick, D.E. Hartmann, Treatment of Wilson's disease with zinc. I. Oral zinc therapy regimens, Hepatology 7 (1987) 522–528.
[12] R.J. Cousins, Absorption, transport and hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin, Physiol. Rev. 65 (1985) 238–309.
[13] G.J. Brewer, G.M. Hill, A.S. Prasad, Z.T. Cossack, P. Rabbani, Oral zinc therapy for Wilson's disease, Ann. Intern. Med. 99 (1983) 314–319.
[14] E.A. Roberts, M.L. Schilsky, A practice guideline on Wilson disease, Hepatology 37 (2003) 1475–1492.
[15] N.F. Krebs, J.E. Westcott, J.W. Huffer, L.V. Miller, Absorption of exogenous zinc and secretion if endogenous zinc in the human small intestine, FASEB J. 12 (1998) A345, 345–348.
[16] H.H. Lee, A.S. Prasad, G.J. Brewer, C. Owyang, Zinc absorption in human small intestine, Am. J. Physiol. 256 (1989) G87–G91.
[17] A. Bernkop-Schnürch, Mucoadhesive systems in oral drug delivery, Drug. Discov. Today 2 (2005) 83–87.
[18] J. Wang, Y. Tabata, D. Bi, K. Morimoto, Evaluation of gastric mucoadhesive properties of aminated gelatin microspheres, J. Control Release 73 (2001) 223–231.
[19] J.A. Fix, R. Cargill, K. Engle, Controlled gastric emptying. Part 3. Gastric residence time of a nondisintegrating geometric shape in human volunteers, Pharm. Res. 10 (1993) 1087–1089.
[20] F. Atyabi, H.L. Sharma, H.A.H. Mohammad, J.T. Fell, In vivo evaluation of a novel gastric retentive formulation based on ion exchange resins, J. Control Release 42 (1996) 105–113.
[21] V. Iannuccelli, G. Coppi, R. Sansone, G. Ferolla, Air compartment multiple-unit system for prolonged gastric residence. Part II. In vivo evaluation, Int. J. Pharm. 174 (1998) 55–62.
[22] S. Sungthongjeen, O. Paeratakul, S. Limmatvapirat, S. Puttipipatkhachorn, Preparation and in vitro evaluation of a multiple-unit floating drug delivery system based on gas formation technique, Int. J. Pharm. 324 (2006) 136–143.
[23] B.Y. Choi, H.J. Park, S.J. Hwang, J.B. Park, Preparation of alginate beads for floating drug delivery system: effects of CO_2 gas-forming agents, Int. J. Pharm. 239 (2002) 81–91.
[24] I. Jiménez-Martínez, L. Quirino-Barreda, Villafuerte-Robles, Sustained delivery of captopril from floating matrix tablets, Int. J. Pharm. 362 (2008) 37–43.
[25] N. Rouge, P. Buri, E. Doelker, Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, Int. J. Pharm. 136 (1996) 117–139.
[26] B.S. Dave, A.F. Amin, M.M. Patel, Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation, AAPS Pharm. Sci. Technol. 5 (2004) A34, 1–6.
[27] P. Sriamornsak, N. Thirawong, K. Korkerd, Swelling, erosion and release behaviour of alginate-based matrix tablets, Eur. J. Pharm. Biopharm. 66 (2007) 435–450.
[28] V. Kudela, Hydrogels, in: Encyclopedia of Polymer Science and Engineering, vol. 7, Wiley, New York, 1987, pp. 703–807.
[29] E. Cedillo-Ramírez, A. Hernández-León, L. Villafuerte-Robles, Effect of added pharmatose DCL11 on the sustained-release of metronidazole from Methocel K4M and Carbopol 971P NF floating matrices, Drug Dev. Ind. Pharm. 32 (2006) 955–965.
[30] W.M. Hlaing, M.D. McCluskeya, A.D. Lalonde, M.G. Norton, Infrared spectroscopy of ZnO nanoparticles containing CO_2 impurities, Appl. Phys. Lett. 86 (2005) 073111, 1–3.
[31] X. Xiaoqiang, S. Minjie, Z. Feng, H. Yiqiao, Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: in vitro and in vivo evaluation in healthy volunteers, Int. J. Pharm. 310 (2006) 139–145.
[32] E. Nürnberg, P. Surmann (Eds.), Hagers Handbuch der Pharmazeutischen Praxis, 5th ed., Bd. 2 Methoden, Springer Verlag, Berlin, 1991, p. 60.
[33] K.A. Kelly, Motility of the stomach and gastroduodenal junction, in: L.R. Johnson (Ed.), Physiology of the Gastrointestinal Tract, vol. 1, 1st ed., Raven Press, New York, 1981, pp. 393–410.
[34] E.A. Klausner, E. Lavy, M. Friedman, A. Hoffman, Expandable gastroretentive dosage forms, J. Control Release 90 (2003) 143–162.
[35] C.R. Rowe, P.J. Sheskey, P.J. Weller, Handbook of Pharmaceutical Excipients, 4th ed., Pharmaceutical Press, London, 2003, pp. 263–265.