Iranian Journal of Pharmaceutical Sciences
Spring 2005: 1(2): 107-114

Original Article

Calcium Acetate Versus Calcium Carbonate as Oral Phosphate Binder: Preparation and *In Vitro* Assessment

Naser Tavakoli[a,*], Abbas Jafarian[b], Farzin Najmi[a]

[a]*Department of Pharmaceutics,*
[b]*Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences,*
Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Calcium acetate is used as an oral phosphate binder to control hyperphosphatemia in patients with chronic renal failure. Compared to calcium carbonate, control of hyperphosphatemia can be achieved at lower calcium administration with calcium acetate which likely reduces the risk of hypercalcemia. In this study, various formulations of calcium acetate tablets were prepared and their disintegration times, dissolution rates and phosphate binding capacities were determined. Dissolution test was carried out using the paddle method according to the United States Pharmacopoeia (USP XXIII). The binding efficiency of the tablets was compared by measuring the amount of insoluble phosphate after mixing with a sodium phosphate solution at pH 6. Calcium acetate tablets had a mean content of 809.6 mg of calcium acetate and a mean weight of 1087 mg. The average breaking load and disintegration times were 66.4±5.5 N and 24.5±2.1 min, respectively. Drug release after 30 and 60 min were 80.45% and 101.42%, respectively. The amount of non-dissolved phosphorus following 60 min incubation of calcium acetate and/or calcium carbonate tablets were 372.8 mg (61.2%) and 463.2 mg (76.0%), respectively. Weight variation, friability, disintegration time, and dissolution rate of calcium acetate tablets were in the acceptable pharmacopoeial limits. A high phosphate binding capacity of calcium acetate tablets indicated that it can be a suitable alternative to calcium carbonate in the management of hyperphosphatemia in patients with chronic renal failure.

Keywords: Calcium acetate; Phosphate binders; Dissolution.
Received: January 12, 2005; *Accepted:* April 10, 2005

1. Introduction

Hyperphosphatemia, a common complication in patients with end-stage renal disease, is treated with oral phosphate binding medications that restrict phosphorus absorption from the gastrointestinal tract [1]. Calcium-containing phosphate binders are used increasingly, instead of aluminum hydroxide [2]. Recent studies on calcium carbonate tablets marketed in the United States and

*Corresponding author: Naser Tavakoli, Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.
Tel (+98)311-7922594, Fax (+98)311-6680011
E-mail: tavakoli@pharm.mui.ac.ir

Canada indicate that many of the products exhibit poor oral bioavailability, despite their wide use [3-5]. On the other hand, some reports have shown that calcium acetate binds phosphorous more effectively than calcium carbonate; therefore, it has many characteristics of an ideal phosphate binder. It is, for instance, a more readily soluble salt compared to calcium carbonate [6-9].

In the present study, we prepared a new formulation of calcium acetate tablet and evaluated its *in vitro* characteristics including disintegration time and dissolution rate as the two most valid indicative tests for *in vivo* performance of calcium tablets. Any impaired product performance, e.g. failure to disintegrate or dissolve in gastrointestinal tract could limit the efficacy of the phosphate binders [10-11]. We further compared the *in vitro* phosphate binding capacity of calcium acetate with that of calcium carbonate tablets. Calcium carbonate tablets (500 mg) are the only calcium-containing phosphate binders marketed in Iran.

2. Materials and methods

2.1. Materials

Calcium acetate, P.V.P K-30, Lactose monohydrate and Magnesium Stearate were from Merck, Germany. Corn starch was from Agena, Austria, and Starch 1500 was from Colorcon, UK. All other chemicals and reagents were USP–NF grade. Calcium carbonate 500 mg tablets were from Tehran Chemie Pharmaceutical Co., Tehran, Iran, and calcium carbonate 1000 mg tablets were prepared in our laboratory in the Faculty of Pharmacy, Isfahan University of Medical Sciences.

2.2. Preformulation studies

The assay of calcium acetate powder was performed according to the British Pharmacopoeia [12]. Water content of calcium acetate powder was measured using Karl Fisher method [12]. The compression properties of calcium acetate powder was determined using Wells' procedure [13]. Briefly, three calcium acetate powder samples weighting 500 mg (A, B and C) were separately mixed with 1% of magnesium stearate by tumble mixing (samples A and B for 5 min and sample C for 30 min). Samples A and C were compressed quickly at 1 ton pressure, held for 2 seconds. For sample B, the load was held at 1 ton for 30 seconds. Crushing strength was determined using tablet hardness tester (Erweka, T.P.A., Germany). The bulk and tapped densities, angle of repose and flow time of granules were determined according to compendial methods [13, 14]. Carrs' index was calculated from the following formula [13]:

Carrs' index = (Tapped density – Bulk density / Tapped density) x 100

2.3. Tableting and physicochemical evaluation of formulations

Systematic preformulation trials were undertaken to study the effects of various binding agents or diluents. Several formulations were prepared, among which six formulations (F1 to F6) were selected for further studies (Table 1). The active ingredient (800 mg) and the filler were granulated in a rotary granulator by adding binder solution (PVP or starch paste), passed through a 12-mesh screen, dried at 140 °F , lubricated and compressed using a Killian R.V.3S rotary press (Kilian & Co., Germany).

2.4. Uniformity of dosage form and assay

Twenty tablets were weighted individually. The average weight was calculated and was compared with the weight of each tablet [15]. The amount of calcium acetate in the tablets was determined using the method of British Pharmacopoeia 23 [12].

2.5. Tablet hardness and friability

Twenty tablets were randomly chosen and their breaking loads were determined

using an Erweka hardness tester instrument (Erweka, T.P.A., Germany). Ten tablets were weighed and placed in the tumbling apparatus of the Roche friabilitor (Erweka, T.B. 24, Germany) where they were exposed to rolling and repeated shocks resulting from free falls within the apparatus (25 rpm, 4 min) [15].

2.6. Tablet disintegration time

Disintegration test was carried out according to the United States Pharmacopeoia (USP 23) method using a Pharma-test (PTZE) disintegration tester [15]. The end point of the test was indicated when the remaining residue had a soft mass with no palpable soft core [15, 16].

2.7. Tablet dissolution test

The dissolution of tablets was measured by the method of USP XXIII (paddle method) using a PTWS3 six-spindle dissolution tester (Pharma-test, Germany). Individual tablets were placed into the vessels containing 0.1 N HCl (37 °C, 75 rpm, 900 ml). Samples (5 ml) were withdrawn from each vessel at 0, 5, 20, 30, 50, 60, 90 and 120 min. Samples were filtered through a 0.22 μm filter membrane. The amount of the dissolved calcium was determined in triplicates at 422.9 nm using a Perkin Elmer 2380 atomic absorption spectrophotometer [15, 17]. The dissolution test was carried out on both 500 mg and 1000 mg calcium carbonate tablets.

The mean dissolution time (MDT) was considered as a basis for the comparison of performances of formulations and was estimated by the following equation [18]:

$$MDT = \frac{\sum_{i=1}^{n} t_{mid} \Delta M}{\sum_{i=1}^{n} \Delta M}$$

Where, t_{mid} is the time between two consecutive sampling and ^{3}M is the cumulative amount of drug dissolved at any time interval.

2.8. Tablet phosphorous binding capacity test

The study model was based on the binding property of the cationic binder with the phosphate [19]. A number of tablets (calcium acetate 800 mg, calcium carbonate 1000 mg and/or calcium carbonate 500 mg) corresponding to 400 mg of elemental calcium were subjected to a 60 min dissolution test in 200 ml simulated gastric fluid without pepsin (containing 2 g of NaCl and 7 ml HCl per liter). After 60 minutes, a solution containing 2.796 g of $Na_2HPO_4.2H_2O$ in 50 ml deionized water was added to the immersion fluid and the pH was adjusted to 6 by NaOH (10 N). After 20 min a 5 ml aliquot of the dispersion fluid was filtered through a membrane filter. A 200 μl sample of this solution was added to 5 ml of a reducing reactive solution (containing 100 g trichloroacetic acid and 6.7 g of L-ascorbic acid per liter) and 0.5 ml molibdic reactive solution (containing 1.62 mmol/l sulfuric acid and 22 g/l ammonium heptamolibdate). The mixture was stirred and left to react for 20 min. The intensity of the created blue color corresponding to the concentration of the insoluble phosphorous was determined spectrophotometrically at 660 nm.

2.9. Statistical analysis

One-way analysis of variance (ANOVA) was used to assess the differences between dissolution rate constants, mean dissolution times and phosphorous binding capacities of different formulations. Student's "t" test was used to compare two means where appropriate. A *p*-value of less than 0.05 was considered significant. Statistical analysis was performed using SPSS 10 for windows.

3. Results

The purity of dried calcium acetate

Table 1. Evaluation of compression properties of calcium acetate powder.

Sample	A	B	C
Mixing time (min)	5	5	30
Applied pressure (ton)	1	1	1
Length of applied pressure (sec)	2	30	2
Mean crushing strength (Newton)	88	100	95

powder, determined according to the British Pharmacoepia, was about 98.4% (w/w). Water content of the calcium acetate powder was 6.1% (w/w). The hardness of the compacts A, B and C was 88, 100 and 95 Newtons, respectively (Table 1). The calcium acetate granules made in our laboratory had the following characteristics: angle of repose = 28.77º, bulk density = 0.675 g/ml, Carr's index = 7.53 and flow rate = 24.41 g/sec.

Tablets in which PVP was used as a binder were superior in terms of hardness and drug release performance. The hardness of formulations (F1-F4) was between 22.25 to 121.30 Newtons (Table 2). However, the compressibility of granules in formulation F5 and F6 was not good enough (hardness <20 Newtons). Based on these findings, the formulation designated as F4 was selected for further experiments.

Calcium acetate tablets (F4) had a mean weight of 1087.1±17.2 mg (1040-1113) and a mean content of 809.6±11.4 mg of calcium acetate. The hardness, friability and disintegration time of tablets were 66.4±9.0 Newtons, 0.548±0.01% and 24.5 min, respectively.

The dissolution of calcium acetate tablets (F4) was performed in 0.1 N HCl and the amount of calcium released was determined by atomic absorption spectrophotometery. To validate the method of analysis, intra-day and inter-day variations were calculated. Coefficients of variations of calcium containing solutions in the concentration range of 10-60 μg/ml was less than 10%. Release behaviors of calcium from calcium acetate tablets and commercially available calcium carbonate tablets are depicted in Figures 1 and 2, respectively. Each data point represents the mean of six determinations. As illustrated, 81.5% of calcium was released from the calcium acetate tablets (F4) within 30 min, which is in accordance with USP 23. However, this amount was 73.4% for tablets prepared using starch paste as binder (F5).

The amount of phosphorous bound as calcium phosphate following 60 min incubation of the calcium tablets in the gastric fluids showed that there were no significant differences ($p< 0.05$) between calcium acetate and calcium carbonate (500 mg) tablets (Table 3). However, both calcium acetate and calcium carbonate (500 mg) tablets showed better phosphorous binding capacity than calcium carbonate (1000 mg) tablets.

4. Discussion

Phosphate binders are a class of compounds that bind dietary phosphorous in

Table 2. Composition of different formulations of calcium acetate tablets.

Ingredients (mg)	Formulation numbers					
	F1	F2	F3	F4	F5	F6
Calcium acetate	800	800	800	**800**	800	800
PVP K-30	100	110	120	**120**	120	-
Sodium saccharine	0.1	0.1	0.1	**0.1**	0.1	0.1
Magnesium stearate	21.7	21.7	21.7	**21.7**	21.7	21.7
Lactose	50	100	150	**200**	-	-
Corn starch	-	-	-	**-**	-	200
Starch 1500	40	40	40	**40**	40	40

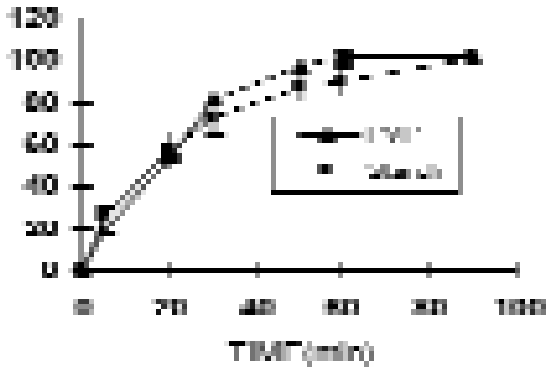

Figure 1. The dissolution profiles of calcium acetate tablets prepared with PVP (▲) and starch (■) binders in 0.1 N HCI, using the paddle method, at 75 rpm, and 37 ºC (n=6).

the gastrointestinal tract resulting in decreased phosphorous absorption and increased fecal elimination of the bound phosphorous. Calcium carbonate has been administered as an effective phosphorous binder for several years. Alternatively, calcium acetate may be used to bind phosphorous in the GIT. In this study, calcium acetate tablets formulated in our laboratory was characterized with regard to the tablet disintegration time, drug release and phosphate binding capacity. The results were then compared with those of calcium carbonate tablets. In some studies, calcium acetate has been shown to possess twice as much phosphorous binding capacity as calcium carbonate, which has been attributed to the greater water solubility of calcium acetate [2, 20-22]. In contrast, some other studies did not show such a significant difference between calcium carbonate and calcium acetate tablets [6-9]. In the present study, we did not observe a significant difference between the phosphorous binding capacity of calcium acetate and calcium carbonate (500 mg) tablets. However, both calcium acetate and calcium carbonate 500 mg tablets showed better phosphorous binding capacities than calcium carbonate 1000 mg tablets. Poor drug dissolution and long disintegration time of calcium carbonate 1000 mg tablets may account for this difference.

Our findings showed that no permanent changes to calcium acetate occurred following compression. It rebounded when the compressive load was released indicating an elastic behavior for calcium acetate powder (Table 1) [13]. Calcium acetate granule characteristics including angle of repose, bulk density, Carr's index and flow rate suggested that the wet granulation method gives suitable granules for tableting.

Among fillers and binders used in this study, lactose as a filler and PVP as a binder produced better results. Starch as a binder caused a high variation in drug release from tablets (Figure 1). Due to the elastic behavior of the calcium acetate powder, the presence of starch or lactose as a filler was necessary to provide sufficient compressibility. However, the friability of tablets in which starch was used was greater than the higher limit accepted by pharmacopoeias [15]. The results of weight uniformity test indicated that all 20 tablets fell within the acceptable limit (mean±5%) by USP.

Tablet disintegration often precedes drug release. Thus the reaction between calcium acetate released from tablet and phosphorous in the gastric acid would be partly dependent on the tablet disintegration time in which the tablet remains in the stomach. Carr and Shangraw [10] showed that 11 of the 21 products tested failed to disintegrate within 30 min. Also, Dal Zotto et al. [23] tested 6

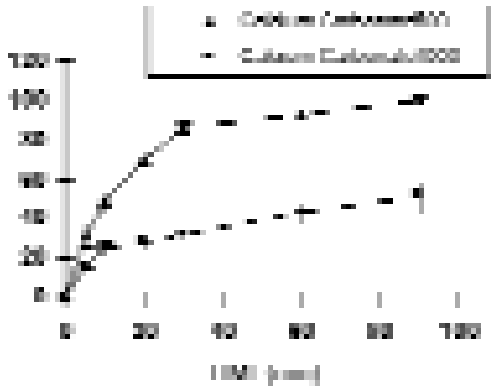

Figure 2. The dissolution profiles of calcium carbonate tablets 500 mg (▲) and 1000 mg (■) in 0.1 N HCI, using the paddle method, at 75 rpm, and 37 ºC.

Table 3. The binding capacity of calcium carbonate and calcium acetate tablets.

Tablets	Elemental calcium (mg)	Phosphorous bound (mg)	Phosphorous bound (%) ± SD
Calcium carbonate (500 mg)*	400.4	463.2	76.0 ± 7.3
Calcium carbonate (1000 mg)	400.4	74.4	12.2 ± 2.9
Calcium acetate (800 mg)*	405.4	372.8	61.2 ± 5.1

* To keep the same amounts of elemental calcium, two tablets of calcium carbonate (500 mg) and calcium acetate (800 mg) were used. All experiments were repeated 3 times.

commercial preparations of calcium carbonate and showed that only three of them were suitable with regard to drug release and disintegration time. In our studies, the disintegration test of calcium acetate tablets which had PVP as binder, showed moderate disintegration time (24.5 min) which was acceptable according to USP [15]. Tablets prepared with starch paste showed similar disintegration time (22.4 min), but with higher variation than those prepared by PVP.

Since drug absorption and physiological availability depend on the available drug in the dissolved state, dissolution is considered as one of the most important quality control tests performed on pharmaceutical dosage forms. Like the disintegration test, the dissolution test provides a means of control in assuring if a given tablet formulation is the same in regard to dissolution as the batch of tablets shown initially to be clinically effective [24]. Brennan et al. [17] in their studies on dissolution of 27 commercially available calcium carbonate supplements showed that at 30 min five preparations (18%) were more than 75% dissolved. Our findings showed that after 30 min 81.5% of calcium was released from calcium acetate tablets indicating that our final formulation met the pharmacopoeial standards in terms of dissolution.

To evaluate the phosphorous binding capacity of the calcium acetate tablets, an experimental model was designed to simulate *in vivo* conditions. A usual dose of tablets (equivalent to 400 mg elemental calcium) was reacted with simulated gastric fluids for 60 min and then was added to 2.796 g of disodium hydrogen phosphate, which was corresponding to the content of a standard meal. The amount of phosphorous bound to calcium acetate tablets (prepared in this study) was 61.2% which is much better than binding capacity of some available phosphorous binders (4-40%) shown by Dal Zotto et al. [23].

The results of our study showed a relatively good correlation ($p<0.05$) between dissolution and phosphorous binding capacity tests performed on calcium acetate and calcium carbonate (500 mg) tablets. However, the correlation of the two tests was poor in the case of calcium carbonate (1000 mg) tablets possibly due to different chemical sources of content (oyster shell versus chemical precipitate).

It is clear that the factors influencing phosphorous binding capacity and hence *in vivo* performance, are complex and that *in vitro* dissolution may not be the only factor predictive of phosphorous binding capacity. Heaney et al. [25] have demonstrated that the bioavailability of calcium has little relationship to the solubility of the calcium salt. They concluded that other factors such as *in vitro* disintegration might be important in determining calcium availability. On the other hand, FDA's report on drug dissolution indicated that problems with drug dissolution account for approximately 80% of the documented drug availability problems [26].

In conclusion, calcium acetate tablet was demonstrated to be an effective phosphate binder *in vitro*, which may predict its effective role *in vivo*.

Acknowledgements

This study was supported by a grant from

the research council of Isfahan University of Medical Sciences, Isfahan, Iran.

References

[1] Bricker NS, Slatapolsky E, Reiss E, Avioli LV.Calcium, phosphorous and bone in renal disease and transplantation. *Arch Intern Med* 1969; 123: 543-53.

[2] Delmez JA, Slatapolsky E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. *Am J Kidney Dis* 1992; 19: 303-17.

[3] Ekman M, Reizenstein P, Teigen SW, Ronneberg R. Comparative absorption of calcium from carbonate tablets, lactogluconate/carbonate effervescent tablet, and chloride solution. *Bone* 1991; 12: 93-7.

[4] Hansen C, Werner E, Erbes HJ, Larrat V, Kaltwasser JP. Intestinal calcium absorption from different calcium preparations: influence of anion and solubility. *Osteoporos Int* 1996; 6: 386-93.

[5] Whiting SJ, Pluhator MM. Comparison of *in vitro* and *in vivo* tests for determination of availability of calcium from calcium carbonate tablets. *J Am Coll Nutr* 1992; 11: 553-60.

[6] Biagini M, Malaguti M, Sicoli R, Capece R, Friggi A, Ciaffi G, Bargagna R. Treatment of uraemic hyperphosphatemia with calcium acetate: a safe alternative to calcium carbonate. *Biomater Artif Cells Immobilization Biotechnol* 1992; 20: 1193-9.

[7] Moriniere P, Djerad M, Boudailliez B, Espern B, Biotte F, Westell PF, Compagnon M, Brazier M, Achard JM, Foumier A. Control of predialytic hyperphosphatemia by oral calcium acetate and calcium carbonate. *Nephron* 1992; 60: 6-11.

[8] d'Almeida Filho EJ, da Cruz EA, Hoette M, Ruzany F, Keen LN, Lugon JR. Calcium acetate versus calcium carbonate in the control of hyperphosphatemia in hemodialysis patients. *Sao Paulo Med J* 2000; 118: 179-84.

[9] Janssen MJ, van der Kuy A, Wee PM, van Boven WP. Aluminum hydroxide, calcium carbonate and calcium acetate in chronic intermittent hemodialysis patients. *Clin Nephrol* 1996; 45: 111-9.

[10] Carr CJ, Shangraw RF. Nutritional and pharmaceutical aspects of calcium supplementation. *Am Pharm* 1987; NS27: 149-57.

[11] Mason NA, Patel JD, Dressman JB, Shimp LA. Consumer vinegar test for determining calcium disintegration. *Am J Hosp Pharm* 1992; 49: 2218-22.

[12] *British Pharmacopoeia 28*. London: The Pharmaceutical Press, 1993; pp. 98-9, A144.

[13] Wells JI. *Pharmaceutical preformulation*. Chichester, West Sussex: Ellis Horwood Limitted, 1988; pp. 209-15.

[14] Aulton EM. *Pharmaceutics, the science of dosage form design*. Hong Kong: Longman Group, 1988; pp. 248-9, 306-7, 313, 603-4.

[15] *US Pharmacopoeia (USP XXIII) /national formulary 18*. Rockville: the United States Pharmacopeial Convention, 1995; pp. 247, 1791, 1838, 1981.

[16] Kobrin SM, Goldstein SJ, Shangraw RF, Raja RM. Variable efficacy of calcium carbonate tablets. *Am J Kidney Dis* 1989; 14: 461-5.

[17] Brennan MJ, Duncan WE, Wartofsky L, Butler VM, Wray HL. *in vitro* dissolution of calcium carbonate preparations. *Calcif Tissue Int* 1991; 49: 308-12.

[18] Gohel MC, Panchal MK. Novel use of similarity factors f_2 and SD for the development of diltiazem HCl modified-release tablets using a 3(2) factorial design. *Drug Dev Ind Pharm* 2002; 28: 77-87.

[19] Sheikh MS, Maguire JA, Emmett M, Santa Ana CA, Nicar MJ, Schiller LR, Fordtran JS. Reduction of dietary phosphorus absorption by phosphorus binders: a theoretical, *in vitro*, and *in vivo* study. *J Clin Invest* 1989; 83: 66-73.

[20] Emmett M, Sirmon MD, Kirkpatrick WG, Nolan CR, Schmitt GW, Cleveland MB. Calcium acetate control of serum phosphorus in hemodialysis patients. *Am J Kidney Dis* 1991; 17: 544-50.

[21] Sousa MF, Abumrad NN, Martins C, Nissen S, Riella MC. Calcium beta-hydroxy-beta-methylbutyrate: 1. potential role as a phosphate binder in uremia, *in vitro* study. *Nephron* 1996; 72: 391-4.

[22] Tavakoli N, Shahidi SH, Baghbani N. Formulation, physicochemical and clinical evaluation of calcium carbonate tablets. Pharm. D. thesis, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, 1999; pp. 55-6.

[23] Dal Zotto M, Ragazzi E, Realdon N, Dalla Fini G. Technological testing of calcium carbonate tablets for use in the treatment of renal osteodystrophy. *IL Farmaco* 1993; 48: 989-1005.

[24] *Remington's Pharmaceutical Sciences*. 19th ed., Pensylvania: Mack Publishing Company, 1995; pp.1641-2.

[25] Heaney RP, Rocker RR, Weaver CM. Absorbability of calcium sources, the limited role of solubility. *Calcif Tissue Int* 1990; 46: 300-4.

[26] Cabana BE, O'Neill R. FDA's report on drug dissolution. *Pharmacopeial Forum* 1980; 6: 71-5.