

INVESTIGATIONS ON THE *IN VITRO* RELEASE MECHANISM OF SODIUM ALENDRONATE FROM HYDROPHILIC MATRIX TABLETS

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Abstract

The aim of this study was to assess both dissolution and release profile of sodium alendronate (AL) from hydrophilic matrix tablets based on different sorts of carbopol with or without chitosan or trimethyl chitosan. There have been prepared three formulations (F1-F3) by direct compression for matrix tablets using as hydrophilic polymer matrix forming 15% Carbopol 71 (C 71), Carbopol 971 (C 971) or Carbopol 974 (C 974).

In parallel, there were prepared two series of three formulations where carbopol has been associated with chitosan (CHT) (F4-F6) or trimethyl chitosan (TMC) (F7-F9). Research results have shown that the introduction of C 974 in the formulation, a highly cross-linked polymer, determined a decrease in the release rate without altering the AL general dissolution and release profile, according to the value of the similarity factor f_2 . The formulations with TMC or CHT have shown superior release properties of AL compared with the formulations F1-F3, having also a different release profile according to the difference factor f_1 and the similarity factor f_2 . Results from data fitting at three mathematical models: zero order, Higuchi model and Korsmeyer-Peppas model, revealed that the introduction of CHT and TMC into the hydrophilic matrix tablets based on carbopol determines AL release by a process of diffusion based on Fick's law.

Rezumat

Obiectivul acestui studiu a constat în evaluarea profilului de dizolvare și cedare a alendronatului de sodiu (AL) din comprimate matriceale hidrofile pe bază de diferite sorturi de carbopol asociate sau nu cu chitozan sau trimetil chitozan. Au fost formulate și preparate, prin comprimare directă, trei formulări (F1-F3) pentru comprimate matriceale, utilizând ca polimer hidrofil formator de matrice 15% Carbopol 71 (C 71), Carbopol 971 (C 971) sau Carbopol 974 (C 974). În paralel, au fost preparate două serii a câte trei formulări în care carbopolul a fost asociat cu chitozan (CHT) (F4-F6) sau trimetil chitozan (TMC) (F7-F9). Rezultatele cercetărilor au evidențiat faptul că introducerea în formulare a C 974, polimer cu grad înalt de reticulare, a determinat o diminuare a vitezei de cedare a AL fără a modifica profilul general de dizolvare și cedare, conform valorii factorului de similaritate f_2 . Formulările în care am asociat CHT sau TMC au prezentat proprietăți de cedare a AL superioare, comparativ cu formulările F1-F3, având de asemenea și un profil de cedare diferit conform valorilor factorului de diferențiere f_1 și a factorului de similaritate f_2 .

Rezultatele obținute prin fitarea datelor pe trei modele matematice: modelul de cedare de ordin zero, modelul Higuchi și respectiv modelul Korsmeyer-Peppas, relevă faptul că introducerea în comprimatele matriceale hidrofile pe bază de carbopol a CHT și a TMC determină o cedare a AL printr-un proces de difuzie bazat pe legea lui Fick.

Keywords: alendronate, matrix tablets, carbopol, chitosan

Introduction

Sodium alendronate is one of the most representative substance from the bisphosphonates class, especially administrated to old patients (65 – 95 years), in order to prevent and treat osteoporosis [1].

Bisphosphonates are synthetic analogues of pyrophosphate present in intra- and extra- cellular medium, as a result of adenosine triphosphate metabolism, deprived by any biological action. The substitution of the oxygen atom with a carbon atom conducted to bisphosphonates, compounds characterized by a high affinity to the bone tissue, thermal and enzymatic stability (fig. 1.).

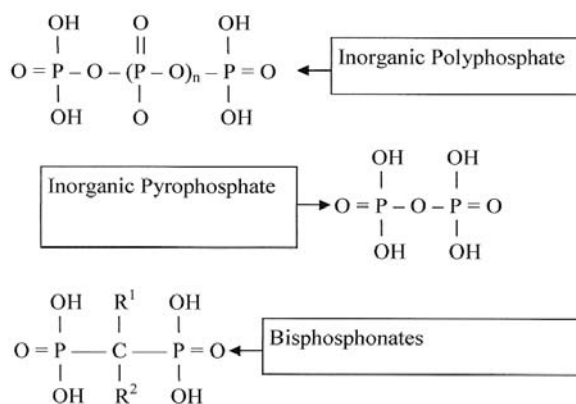


Figure 1

General structure of bisphosphonates

Due to the nature of the substituents, we can distinguish between:

- *bisphosphonates without nitrogen atom inside the molecule:* etidronate, clodronate, tiludronate;
- *aminobisphosphonates:* pamidronate, alendronate, neridronate;
- *aminobisphosphonates with substitution of the nitrogen atom:* olpadronate, ibandronate;
- *bisphosphonates basic heterocycles containing nitrogen:* risedronate (the pyridine ring), zoledronate (imidazol ring) [2 - 4].

In the last three decades, this class of therapeutical agents has been widely studied, being formulated and prepared new pharmaceutical products recommended in some different bone diseases.

At present, bisphosphonates represent the first choice medication in treating all types of osteoporosis.

The main disadvantage of the bisphosphonates is the minimal intestinal absorption, below 1% up to a maximum 10%, depending on the chemical structure, the administrated dose and the administration route [5].

Structurally, there are two important characteristics that limit the oral bioavailability of bisphosphonates: low lipophilia that limits transmembranary transport and also high polarity which prevents paracellular transport. Bisphosphonates absorption is also negatively influenced by food presence, especially rich calcium food or other bivalent ions with whom bisphosphonates form insoluble chelates. Also, the oral bioavailability of bisphosphonates is reduced by the presence of other foods at the gastrointestinal tract level, like fruit juice, coffee, etc. [6-7].

Nowadays, studies for the oral bioavailability optimisation of bisphosphonates are oriented towards two major directions: the increase of the lipophilic character by structural modifications and the formulation in different modified release dosage forms [6, 8-9].

The formulation of alendronate (AL) in matrix tablets based on different types of Carbopol (C), associated or not with Chitosan (CHT) or N – trimethyl chitosan (TMC) conducts to obtaining some therapeutical systems with slow release which could generate an increase of the oral bioavailability of the active substance.

In order to obtain hydrophilic matrix tablets, in this study we used three sorts of C: Carbopol 971 C (C 971), Carbopol 71 G (C71) and Carbopol 974 G (C974). The general structure of the carbopol polymer is shown in fig. 2.

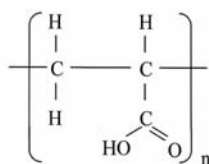


Figure 2

General structure of carbopol polymers

Although C 971 and C 974 are obtained by a similar technological process, the difference between them is the fact that C 971 sort has a low level of crosslinking agent, compared to C 974. C 71 is the granular form of C 971 recommended to be used in direct compression [10-12].

CHT (poly- $[\beta\text{-(1-4)-2-amino-2-deoxy-D-glucopyranose}]$) (fig. 3.) is a cationic biodegradable polysaccharid obtained by the partial deacetylation of chitine, a natural substance which is present in crustacean shell [13].

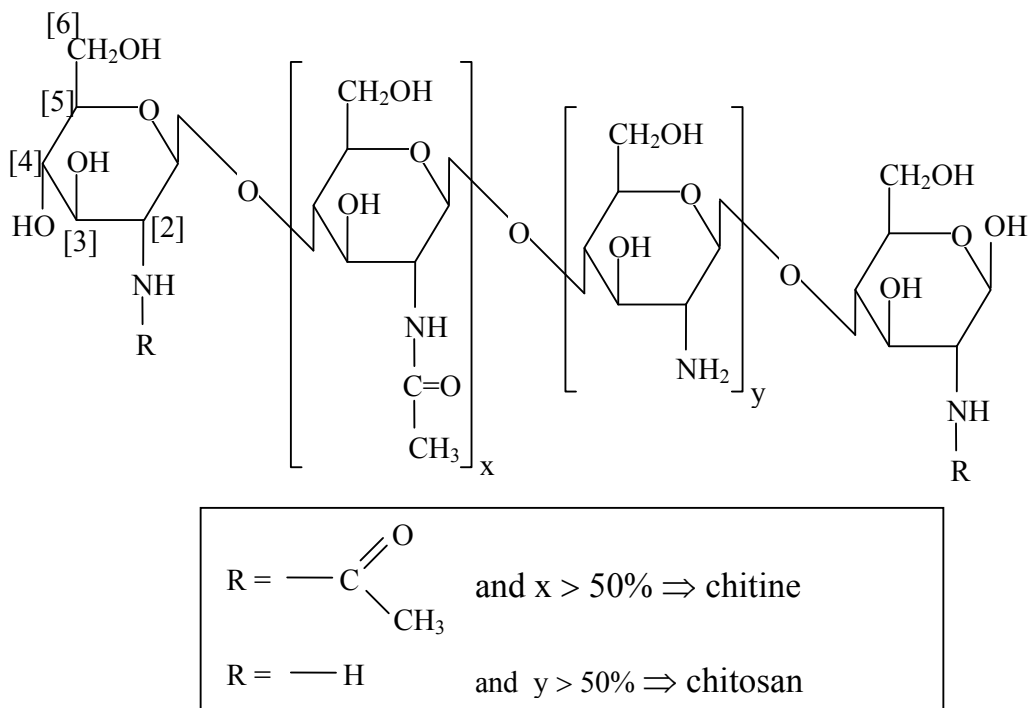


Figure 3
Chemical structural of chitine and chitosan

Chitosan and its derivatives are substances which are very studied in the pharmaceutical technology, being used as forming excipients of matrix tablets with modified release. At low pH values, CHT is soluble while the sol-gel transition occurs at approximately $\text{pH} = 7$. CHT derivatives have been evaluated to overcome the limited solubility of CHT at neutral pH. The pH sensitivity, coupled with the reactivity of the primary amine groups that have a pK_a in the range of 5.5 – 6.5, make CHT a unique polymer for oral drug delivery applications [14-15].

The main objective of this study is to investigate the influence of the type of C, CHT and TMC onto the release kinetics of AL from the hydrophilic matrix tablets.

Materials and methods

Materials

Sodium trihydrate alendronate (Apotex Pharmaceuticals INC, USA), *Carbopol 974 P NF*, *971 P NF*, *71 G NF* (Noveon Inc., USA), *Ludipress LCE* (BASF), *Aerosil 200* (Degussa), *Magnesium stearate* (Union Derlivan S.A. Spain), *Chitosan high molecular weight* (degree of deacetylation > 85 %, Aldrich, Germany), *N – Trimethyl Chitosan* (G.L.S. Chemicals & Materials, India).

Methods

Matrix tablets preparation

There have been formulated nine matrix tablets with AL which have been obtained by direct compression with the *Korsh EKO* tableting machine (punch diameter of 9 mm, compression pressure of 8-10 kN). Formulations noted with F1, F2, F3 contain as matrix polymer 15% C 71 (F1), 15% C 971 (F2) while formulation F3 contains 15% C 971 + 2% C 974. Furthermore, formulations F4 - F6 contain 6% CHT, while formulations F7 - F9 contain 6% TMC.

"In vitro" dissolution studies

In vitro dissolution tests have been performed using a *SR 8 Plus Series* (AB & L Jasco) device, according to the following experimental protocole: *dissolution medium*: 900 mL of simulated gastric fluid (pH 1.2, HCl 0.1N) for the first 2 hours and 900 mL simulated intestinal fluid (pH 6.8 - phosphate buffer) for the next 10 hours; *Apparatus 2 (paddles)*; *bath temperature* 37°C±0.5 °C; *rotation speed*: 50 rpm; sampling interval has been set at every hour for 12 hours. There were taken 7mL of sample each hour and they were simultaneously replaced with the same volume of medium. One sample from the aliquot was subjected to the derivation and dosage procedure described in the USP monography for the HPLC analysis of Sodium Alendronate. The quantitative determination equipment included the following modules: HPLC type HP 1090 series II provided with a diode array detector, UV-VIS spectrophotometer Agilent technologies 8453 and Zorbax C18 column. The mobile phase was a mixture of methanol, acetonitrile and water in the following proportions: 17.5:17.5:65. Mobile phase flow was set at 0.3 mL/min., the injection volume was 20µL and the detection was performed at 266 nm [16]. All the experiments were performed in triplicate.

The analysis of the difference factor (f_1) and the similarity factor (f_2)

The difference and similarity factors between the formulations F1-F3 and the formulations that contain CHT (F4 – F6) and TMC (F7 – F9) respectively, have been determined based on the obtained data during the dissolution tests. The results have been analyzed according to equations 1 and 2:

$$f_1 = \left\{ \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \right\} \times 100 \quad (1)$$

$$f_2 = 50 \log_{10} \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

where: n = the number of sampling time points, R_t = released AL percentage of the reference formula at time point t , T_t = released AL percentage of the test at time point t and $\log_{10} x$ represents the logarithm of x to the base 10 [17].

Data fitting

The investigation of AL release from the hydrophilic matrix tablets based on carbopol polymers has been performed through the analysis of the data results after performing the dissolution test, according to the following mathematical expressions: zero order equation 3, Higuchi model equation 4 and Korsmeyer-Peppas model, respectively equation 5:

$$M_t = M_0 + K_0 t \quad (3)$$

$$M_t = M_0 + K_H t^{0.5} \quad (4)$$

$$M_t = M_0 + K_K t^n \quad (5)$$

where: M_t = the amount of the drug dissolved at time t , M_0 = the initial amount of drug in the solution, K_0 = zero order rate constant, K_H = Higuchi rate constant, K_K = Korsmeyer - Peppas rate constant and n = the release exponent which characterizes the mechanism of drug release [18-20].

The simulation analysis, plotting and data fitting have been performed using Matlab 7.1 software.

Results and discussion

Dissolution test results showed that CHT determined a slight optimization of the release characteristics of matrix tablets based on Carbopol (Fig. 4). The values of f_1 and f_2 presented in Table I reveal that the dissolution profile is different in formulations F4 and F5 compared with

formulations F1 and F2. Comparative analysis of formulation F6 as test and F3 as reference formulation led to a value of f_2 similarity factor higher than 50 ($f_2 = 57.187$), which means that CHT does not change the dissolution profile in F6. We assume that the mechanism by which CHT influences AL release is based on the low CHT solubility at pH = 6.8 and in the case of formulation F6 occurs C974 polymer influence which, due to the high crosslinking degree leads to a slower hydration of the matrix tablet. In this context we can say that between CHT and C 974 it is a synergy of action on the AL release profile of the hydrophilic matrix tablets with slow release.

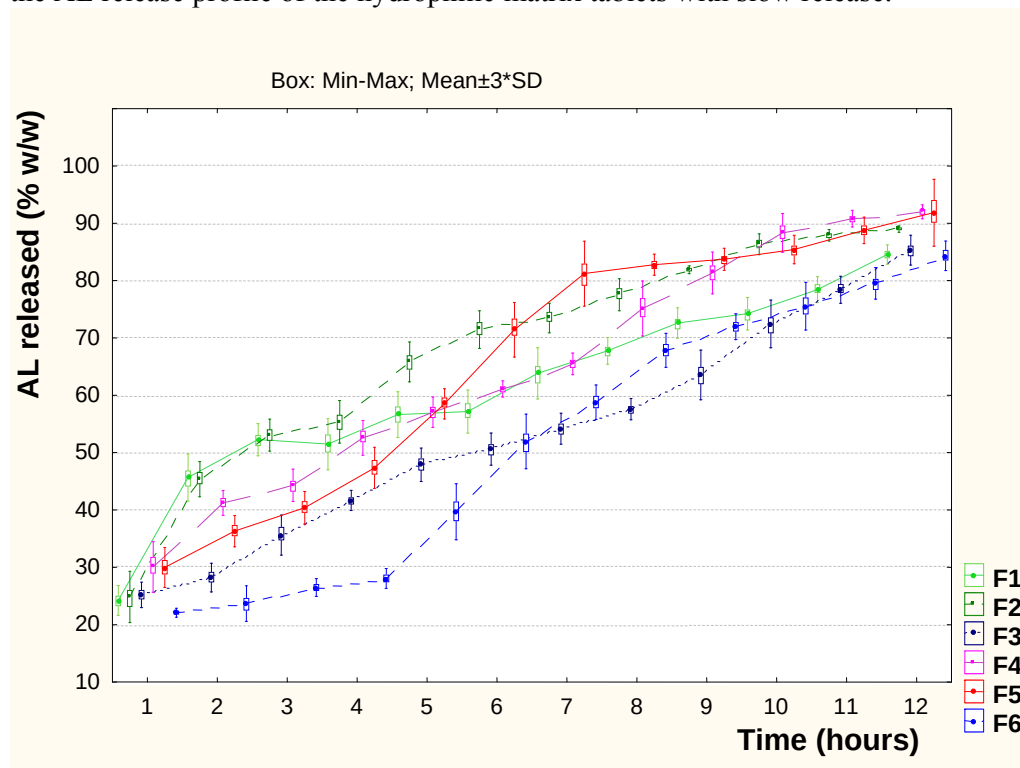


Figure 4
AL dissolution profile from the formulations F1 – F6

Table I
Values of the difference factor f_1 and the similarity factor f_2
(Reference formulas F1 – F3 versus F4 – F6, as test formulas)

Reference formula (R _i)	Test formula (T _i)	f_1	f_2
F1	F4	28.991	31.947
F2	F5	12.422	46.748
F3	F6	10.799	57.187

Comparative results of formulations F7 - F9 containing TMC to formulations F1 - F3 are shown in Fig. 5.

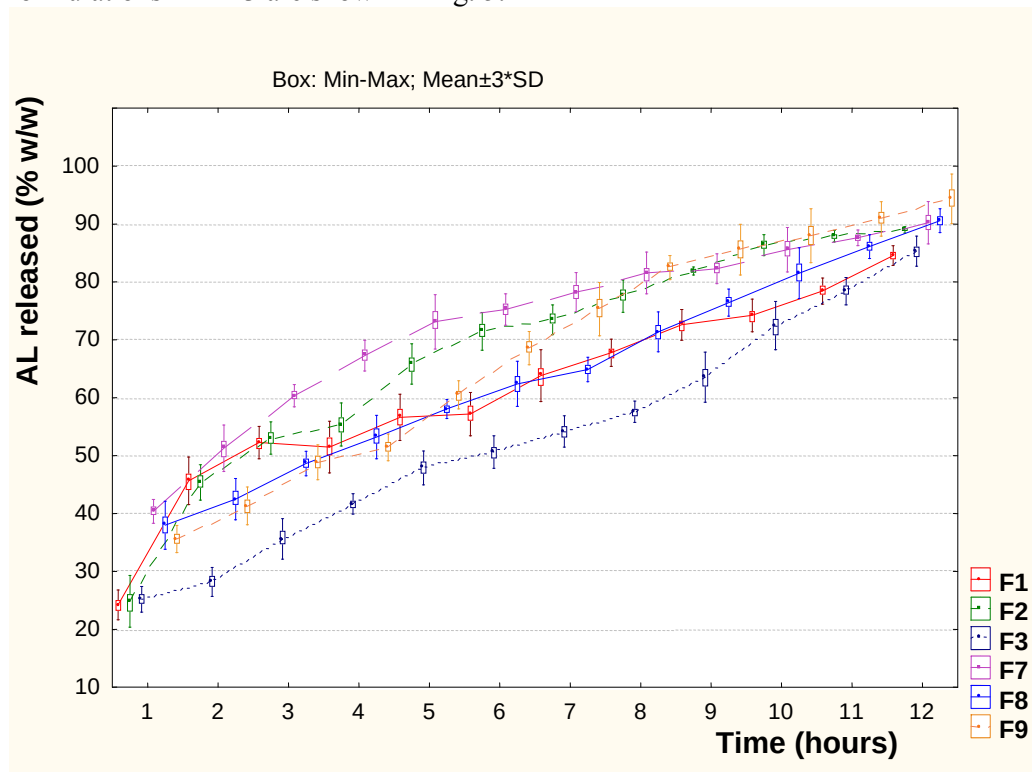


Figure 5

AL dissolution profile from the formulations F1-F3/F7-F9

TMC determined an increase of the release rate of the active substance from the beginning, influence that can be observed during the whole 12 hours test, the final percentage of released the AL from the formulations F7-F9 being higher, over 90%, comparatively to formulations F1-F3.

The presence of C 974, a highly crosslinked polymer in formulation 3, determines an increase of the release kinetics of AL from the matrix tablets (fig. 4) without modifying the release profile, according to the value of the similarity factor ($f_2 = 50.94$) if F1 is the reference formula and F3 is the test formula. In F9, this phenomenon is no longer present, TMC having a significant influence on the release profile, the values of the similarity factor f_2 being under 50 for the series of formulations F7-F9 (Table II).

Table II

The values of the difference factor f_1 and the similarity factor f_2
(Reference formulas F1 – F3 versus F7 – F9, as test formulas)

Reference formula (R _i)	Test formula (T _i)	f_1	f_2
F1	F7	23.247	39.942
F2	F8	13.119	47.307
F3	F9	27.969	39.230

The results obtained at data fitting with the three selected mathematical models prove that AL release from the hydrophilic polymeric matrix tablets takes place by diffusion and erosion without any statistical differences between the studied formulations. We noticed that the introduction in the formula of CHT and TMC increased the influence of the erosion phenomenon on the release process ($n = 0.310 - 0.428$).

The regression coefficients and the constants of the equations that have been obtained based on the selected mathematical models are shown in Table III.

Table III

AL release kinetic constants from hydrophilic matrix tablets

Formula	Zero order		Higuchi model		Korsmeyer-Peppas model		
	K_0	R^2	K_H	R^2	n	K_K	R^2
F1	4.395	0.955	20.645	0.972	0.422	29.049	0.961
F2	6.574	0.970	30.950	0.989	0.536	28.235	0.988
F3	5.306	0.992	24.135	0.978	0.504	21.805	0.979
F4	3.935	0.940	18.940	0.980	0.310	42.850	0.992
F5	4.725	0.998	21.554	0.986	0.351	35.260	0.975
F6	5.706	0.986	26.405	0.989	0.428	32.548	0.980
F7	3.935	0.940	18.940	0.980	0.310	42.850	0.992
F8	4.725	0.998	21.554	0.986	0.351	35.260	0.975
F9	5.706	0.986	26.405	0.989	0.428	32.548	0.980

R^2 = regression coefficient

Conclusions

The outcomes of this study prove that AL release from hydrophilic matrix tablets based on carbopol, takes place by diffusion or erosion, the introduction of CHT or TMC in the formulation determining a major influence on the diffusion phenomenon according to Fick's law ($n < 0.45$). The introduction in formulation of C 974, a highly crosslinked polymer, determined a decrease of AL release, without modifying the general release profile, according to the similarity factor f_2 . The formulations where we associated CHT (F4 - F6) or TMC (F7 – F9) proved an increase of AL release kinetics compared to formulations F1 – F3. The values of f_1 and f_2

factors show that the release and dissolution profile of AL from the studied matrix tablets is influenced by CHT and TMC, excepting the association of CHT with C974 in F6 which has not modified the dissolution profile.

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