Thermal Stability of Sodium Alendronate in a Mixture with Cross-linked Acrylic Acid Polimers and Chitosan

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Thermal stability of alendronate sodium in a mixture with cross-linked acrylic acid polimers and chitosan, formulated and preparated as oral matrix systems, was qualitatively evaluated by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and infrared spectroscopy (FT-IR). The results of the study have shown alendronate stability in association with carbopol and chitosan. DTG curves and FT-IR results suggest certain interactions between carbopol and chitosan, most probably ionic and hydrogen bonds. We consider that the nature and intensity of these bonds could be a positive factor decreasing pH dependence of Carbopol in releasing drug substance.

Keywords: alendronate, carbopol, chitosan, thermal analysis

Alendronate sodium is the orally bioavailable form of alendronic acid, a second generation geminal bis-phosphonate, approved for treating post-menopausal osteoporosis, osteoporosis in men and as therapy of glucocorticoid induced osteoporosis [1].

Orally administrated, alendronate is characterised by a very low bioavailability, less than 1%. Alendronate' s gastro-intestinal absorption window is situated in the upper part of the intestinal tract (duodenum ans jejunum), at pH 6. Alendronate formulated as matrix hydrophilic tablets based on carbopols only or associated with chitosan could assure a prolonged release of it and consequently, an increased bioavailability [2, 3].

Carbopols are cross-linked acid acrylic polimers having optimal characteristics for formulation as hydrophilic matrix systems with prolonged release.

In this study we used Carbopol 971P NF, Carbopol 71G NF (granulated formula of Carbopol 971, with improved flow properties but the same cross linking degree), Carbopol 974P NF.

In contact with dissolution media the external surface of carbopol matrix tablet hydrates, swells and form a hydrogel layer which controls the release of drug substance. Hydration and swelling rate of carbopol polymers depends on moleculare structure and on cross linking degree of each individual polymer, as well as on pH value of dissolution media [4].

Chitosan is a natural cationic polysaccaharide obtained by the partial deacetilation of chitin. Due to its properties this biodegradable and biocompatible polymer is thought to be an excelent excipient for oral pharmaceutical forms [5].

We also consider that by different characteristic mecanisms, chitosan could improve alendronate bioavailability from hydrophilic matrix tablets.

The aim of this study is the evaluation of the thermal stability and behaviour of alendronate and compressed polymers mixture, concerning preparing prolonged release hydrophilic matrix tablets, based on three carbopol types. In three formulations we indroduced chitosan as an absorbtion promoter.

Experimental part

Materials and methods

Alendronate sodium trihydrate (courtesy of Apotex Pharmaceutics INC), *Carbopol 974 P NF, 971 P NF, 71 G NF* (Noveon Inc.), *Ludipress LCE* (BASF), *Aerosil* 200 (Degussa), *Magnesium stearate* (Union Der1ivan S.A. Spain), *Chitosan* high molecular weight (degree of deacetylation > 85 %, Aldrich).

Formulation and preparation of matrix tablets: Six tablet formulation (Table I) were prepared by direct compression method using a *Korsch EK0* tabletting machine with two stations (9 mm flat punches, compression pressure of 8-10 kN).

Subsequently, the tablets were ground with a ball grinder and mixture powders corresponding to six formulations and raw materials were qualitatively assessed by:

Differential scanning calorimetry (DSC) carried out with a Pyris Diamond DSC Perkin Elmer, USA under the following experimental conditions: the samples (4 - 4,5 mg) sealed in an aluminum pan and heated at a constant rate of 10 °C/min were analysed in dynamic regime at a temperature range of 50-300°C. Through measurement cell was maintained an inert atmosphere by purging nitrogen at a flow rate of 20 ml/min. Before the study, the calorimeter was calibrated, in order to measure the temperature and the energy, using Indium as standard.

Thermogravimetric analysis was performed using a derivatograph Mettler Toledo TGA-SDTA 851 e, in a nitrogen atmosphere with a flow rate of 20 mL/min, with a heating speed of 10°C/min (25-600°C) having sample weight of 3-6 mg.

FT-IR spectra were obtained with a Vertex 70 FT-IR spectrometer (Bruker, Germany), using the KBr pellets technique. For each sample, 32 scans were colected in the absorbance mode and transformed. Obtained spectra were compared with those available in the scientific literature [6].

Results and discussions

In analysis of the obtained results we will refer more to the formula F6 because it is representative for this study,

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Table I
ALENDRONATE HYDROPHILIC MATRIX TABLET FORMULATIONS

%/tab.	F1	F2	F3	F4	F5	F6
Carbopol 71	15	-	-	15	-	-
Carbopol 971	-	15	15	-	15	15
Carbopol 974	-	-	2	-	-	2
Alendronate sodium	13.05	13.05	13.05	13.05	13.05	13.05
Mg stearate	0.5	0.5	0.8	0.5	0.5	0.8
Aerosil	-	0.5	1.5	-	0.5	1.5
Chitosan	-	-	-	6	6	6
Ludipress LCE	71.45	70.95	67.65	65.45	64.95	61.65
Total	100	100	100	100	100	100
W tab (mg)	200					

including all substances under study (considering structural indentity between Carbopol 971 and Carbopol 71).

From the analysis of DSC thermograms, figure 1.a. and b., we observe that alendronate has the melting point at aproximatively 129 °C both in pure state and in compressed mixture. This observation is standing for all six analised formulations, in figure 1 a. and b. being shown only DSC thermograms for formulations F3 and F6. DSC results suggest that alendronate isn' t strongly bonded, by physical bonds, to other constituents of matrix tablets. Powders mixtures have good thermal stability in compression, detecting a thermal oxidation process which starts at 220 °C, proved by the maximum exotherm.

Thermogravimetrical characteristcs for alendronate and the six formulations obtained by thermogravimetric analysis are shown in table 2.

T_{onset}: degradation starting temperature at every stage; **T_{peak}:** temperature at which the degradation rate is maximum; **T_{endset}:** degradation ending temperature at every stage; **W_{loss}**: mass loss at every stage; **Wres:** residual weight at 600°C.

DTG curve, figure 2, indicates the presence of alendronate maximum characteristic in the range of 127-135 °C, both in pure substance as well as, in the mixture of formula F6. Regarding carbopol polymers we observe characteristic peaks of Carbopol 971 and Carbopol 974

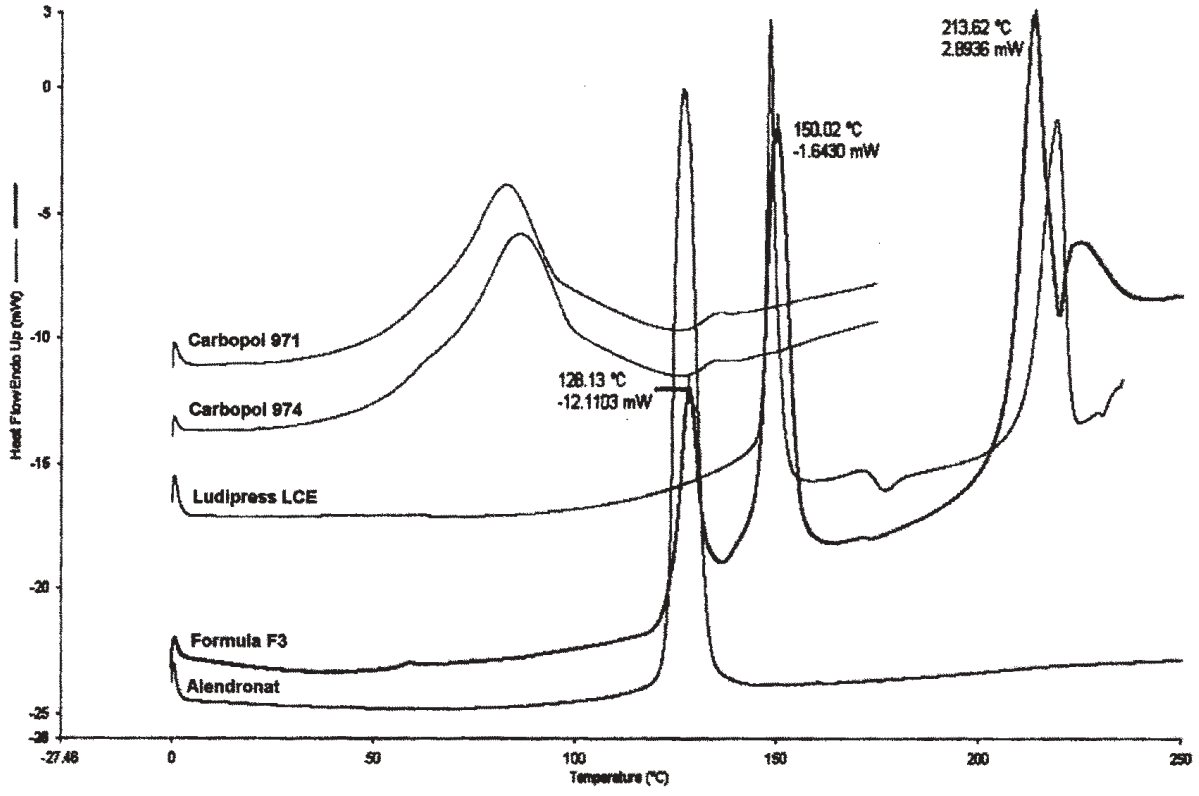

Fig. 1. a. DSC Termograms – Formula F3

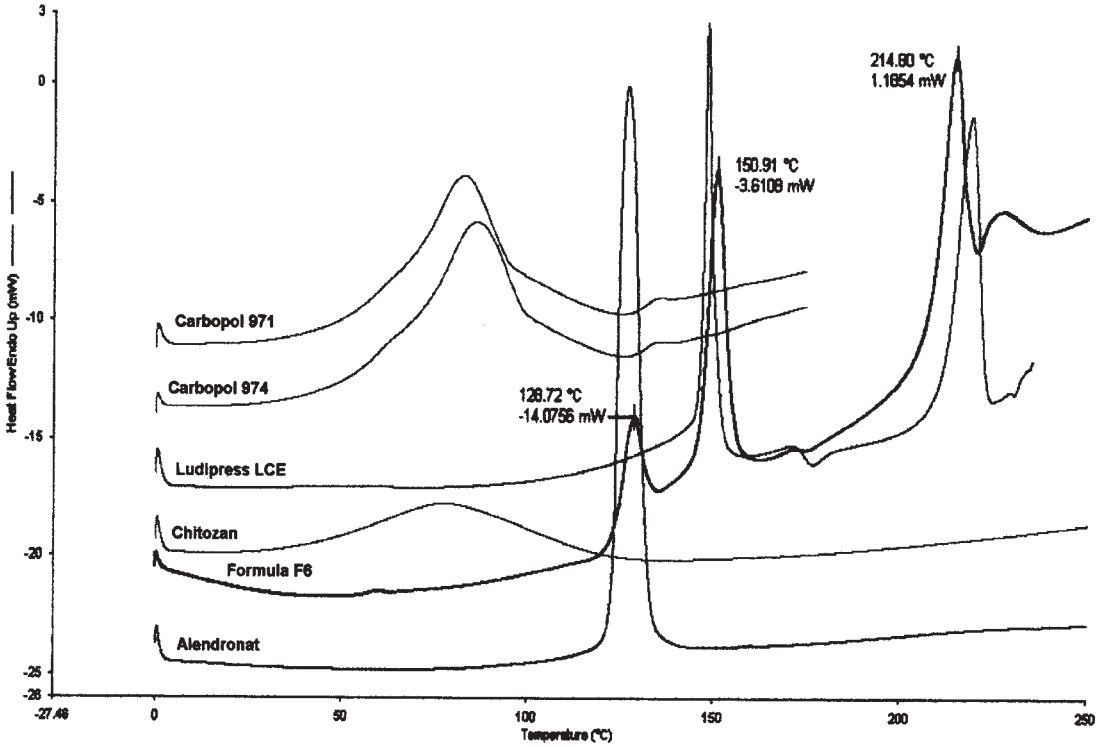

Fig. 1. b. DSC Termograms DSC – Formula F6

Table 2

THERMOGRAVIMETRICAL CHARACTERISTICS OF ALENDRONATE AND FORMULAS **F1-F6**

Sample	Stage	T_{onset}	T_{peak}	T_{endset}	W_{loss}(%)	W_{res} (%)
Alendronate sodium	I	99	127	135	16.33	55.93
	II	244	331	390	16.91	
	III	390	404	443	10.83	
F1	I	45	48	117	0.74	35.58
	II	117	137	153	5.32	
	III	212	225	256	18.55	
	IV	256	266	280	19.63	
	V	280	403	486	20.18	
F2	I	48	57	123	1.22	37.18
	II	123	140	154	5.15	
	III	216	226	248	17.71	
	IV	248	269	280	15.88	
	V	280	412	463	22.86	
F3	I	50	54	115	2.45	32.97
	II	115	140	153	5.47	
	III	213	223	266	19.65	
	IV	266	270	281	13.71	
	V	281	418	475	25.75	
F4	I	50	58	121	2.48	33.84
	II	121	140	150	4.69	
	III	208	220	251	16.85	
	IV	251	268	278	14.38	
	V	278	414	462	27.76	
F5	I	50	57	121	1.42	38.84
	II	121	139	151	4.67	
	III	212	222	255	16.09	
	IV	255	269	276	14.58	
	V	276	408	455	24.40	
F6	I	50	63	121	4.22	29.77
	II	121	138	147	6.86	
	III	211	222	272	18.83	
	IV	272	269	313	16.57	
	V	313	426	482	23.75	

***T_{onset}:** Degradation starting temperature at every stage; **T_{peak}:** Temperature at which the degradation rate is maximum; **T_{endset}:** Degradation ending temperature at every stage; **W_{loss}**: Mass loss at every stage; **Wres:** Residual weight at 600°C;*

displacement from 248°C and respectively 246°C, around the value of 222°C.

Also, the maximum characteristic of chitosan at 302°C isn' t found in DTG curve of formula F6.

These displacements could be determined by the appearence of some bonds between chitosan and carbopol polymers.

1. Alendronate; 2. Chitosan; 3. Carbopol 971; 4. Carbopol 974; 5. Formula F6

Scientific information which discuss carbopol polymers mixtures with different substances show certain displacement of carbopol polymer spectrum as a consequence of interacting by hydrogen bonds.

In our case FT-IR spectrum have shown that the specific carbonil peak (1712 cm^{-1} νC=O includes two absorptions : C=O free – 1740 cm^{-1} and C=O associated – 1712 cm^{-1}, analysis performed by prin curve-fitting) from carbopol remains almost the same in the studied formulations, as we can observe in figure 3a and 3b. Chitosan spectrum shows a certain change: 1651 cm^{-1} peak characteristic to primary amide group couldn' t be clearly identifed in the formula F6 spectrum.

Alendronate is clearly observed on the spectrum of formula F3 and F6, only from 1545 cm^{-1} peak, but it isn't so intense as the absorption of phosphate group from the alendronate analysed as pure substance (figs. 3a and 3b).

Alendronate has a very well structured absorption peak also around 3000-3600 cm^{-1}, when the 3487 cm^{-1} peak is given to hydroxyl free groups from the phosphate, 3345 cm^{-1} at ν_{asym} NH_2 and 3245 cm^{-1} at ν_{sym} NH_2. In the spectrum of mixtures, there can also be identified peaks at

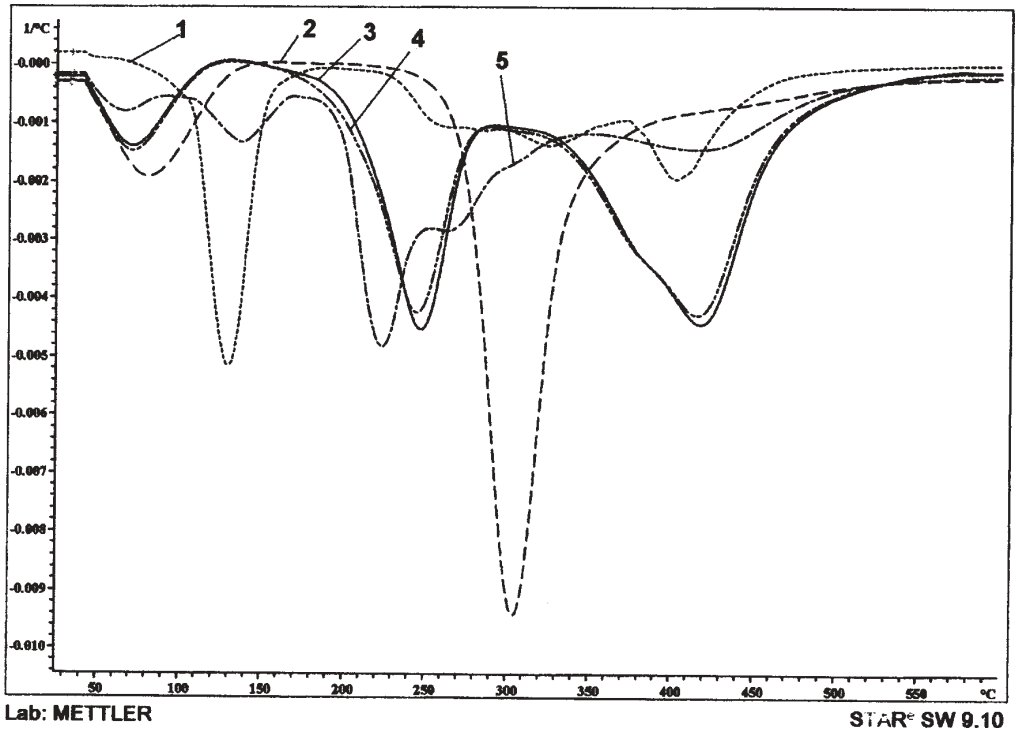

Fig. 2. DTG Curves –Formula 6. 1. Alendronate; 2. Chitosan; 3. Carbopol 971; 4. Carbopol 974; 5. Formula F6

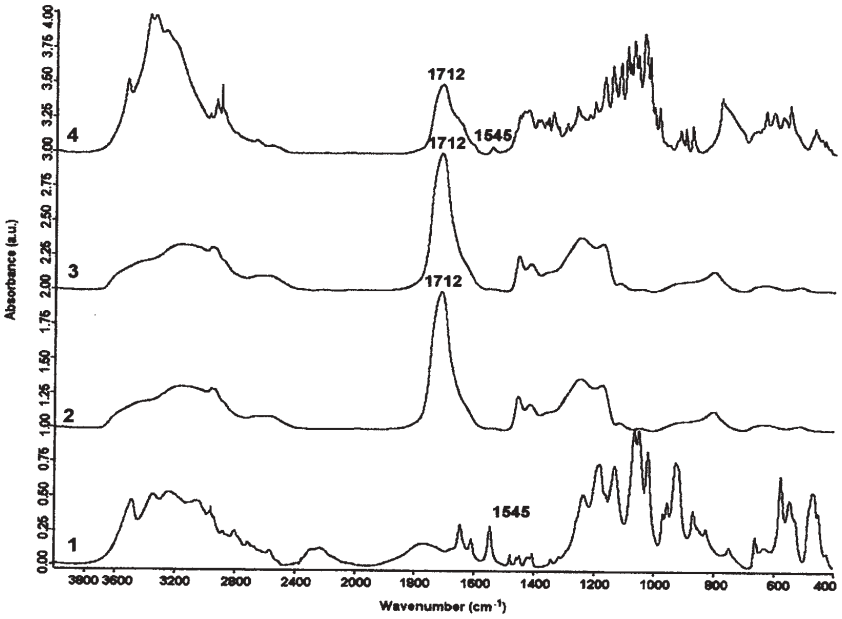

Fig. 3a. FT-IR spectra – Formula 3 1.Alendronate; 2. Carbopol 974; 3. Carbopol 971; 4. Formula F3

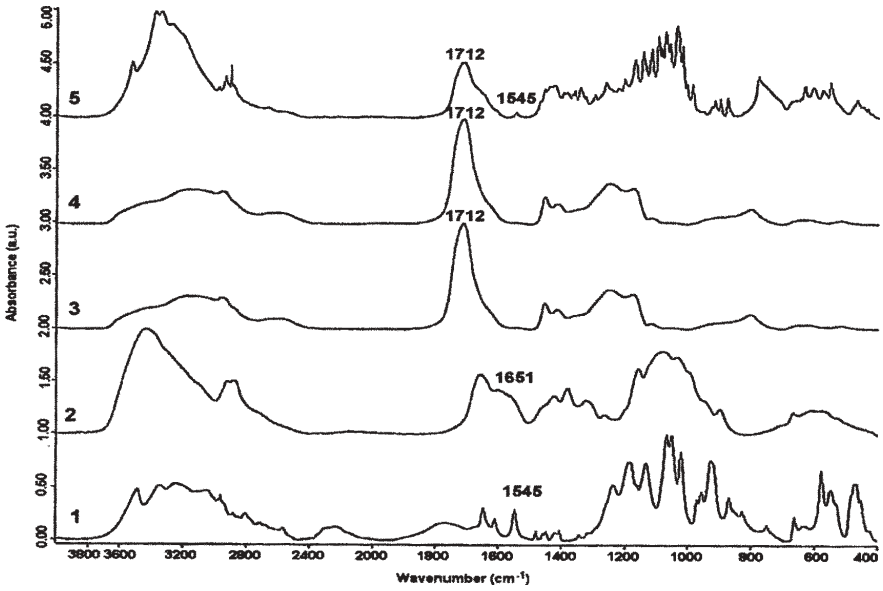

Fig. 3b. FT-IR spectra – Formula 6 1. Alendronate; 2. Chitosan; 3.Carbopol 974; 4. Carbopol 971; 5. Formula F6

3528 cm^{-1}, characteristic for hydroxyl free groups from the Ludipress LCE excipient.

However, Ludipress LCE spectrum shades the other absorbtions which makes difficult to recognise other groups or other types of bonds.

Conclusion

The experiments of this study have confirmed the stability of alendronate in association with carbopol polymers and chitosan. All three methods of thermal analysis have shown the identical characteristics of alendronate pure in the final results of formulations F1-F6, as following:

-DSC thermograms prove a melting point at 129 °C;

-DTG curves show a characteristic maximum at 127-135 °C;

-FT-IR spectrum shows at 1545 cm^{-1} specific peak to phosphate group from alendronate.

Also, the obtained results confirm the hypothesis of certain interactions between $-COO^-$ groups from carbopol and $-NH3^+$ from chitosan. This phenomenon can be a positive mean in deacreasing *p*H dependance of carbopol in releasing drug substance, leading to the right premise in continuation of the study upon the cinetic release of alendronate from hydrophilic matrix tablets characterised in this material.

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