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Oxidative stability of semi-solid excipient mixtures with corn oil and its implication in the degradation of vitamin A

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Abstract

In this work the results obtained from studying accelerated oxidation of semi-solid excipient mixtures which contain corn oil, as vehicles for hard gelatin capsule filling, are compared with the oxidative degradation of vitamin A in the encapsulated formulations. In the first phase the Rancimat procedure was employed to evaluate the oxidation of the excipient mixtures in accelerated conditions, and in the second a real-time study was carried out on the encapsulated formulations using vitamin A as a model substance to test the oxidative resistance of the dosage form. The results show the influence of the percentage of corn oil and temperature storage on the stability of vitamin A and the relative effectiveness of BHA/BHT mixture. HPLC method was used for the quantitative determinations of vitamin A. © 1997 Elsevier Science B.V.

Keywords: Corn oil; Oxidation; Vitamin A; Semi-solid-lipid matrix; Self-emulsifying delivery system; Capsules

1. Introduction

Hard gelatin capsules are nowadays a common pharmaceutical means of oral administration of pharmaceutical formulations. Known since the beginning of the century (Augsburger, 1990), they have traditionally been used for the administration of solid substances, but recent decades have seen substantial advances in the use of new excipient mixtures for filling the hard gelatin capsules and in the technology of their manufacture, both in filling equipment and in the design and sealing of the gelatin shells, which have widened the field of application of this pharmaceutical form to liquid and semi-solid materials.

Recent advances in the formulation of semi-solid bases for hard gelatin capsule filling tend to use mixtures based on vegetable oil (generally seed oil) and surfactants to carry certain active

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principles which are difficult to dissolve, thus improving their gastric tolerance, modulating their cession, and even in some cases improving their bioavailability (Halbaut et al., 1995a). The bibliography refers to the use of vegetable/derived glyceride/surfactant semi-solid-lipid matrix (Kinget and De Greef, 1994) and the physical/chemical studies applicable to the development of vegetable-oil/polyethylene glycol/surfactants self-emulsifying systems (Kinget and Van Roelen, 1994; Halbaut et al., 1996).

In addition to the usual considerations in any form of oral administration, two specific points must be borne in mind in the development of this type of formulation. One is the physical stability of the encapsulated masses, since leakage may occur (Halbaut et al., 1995b). Another is the stability against oxidation since vegetable oils are liable to undergo autooxidation, especially those which contain a high percentage of unsaturated fatty acids (Frankel, 1995).

The mechanisms which govern lipidic oxidation have been widely studied. According to the theory of radicals, autooxidation begins with the appearance of free radicals in the polyunsaturated fatty acids as shown in the plan below.

Once produced, the alkyl radicals ($R^{\cdot}$) react very rapidly with oxygen to form peroxyl radicals ($ROO^{\cdot}$). These peroxyl radicals propagate a chain reaction by reacting more lipids to produce hydroperoxides (ROOH). These hydroperoxides decompose readily to form secondary oxidation products.

The oxidation process comprises three stages: in the induction phase almost no secondary products are formed. The break-up of the hydroperoxides supposes a rapid autocatalytic phase, during which oxygen consumption and peroxide increase are very important, and in which volatile products begin to be detected. The final phase is saturation or paralysation.

Concerning the two semi-solid mixtures above mentioned, with high vegetable-oil content, oxidation process of the oil may be modified by the other components of the formulations. In this regard it must also be borne in mind that preparation is usually carried out at relatively high temperatures. On the other hand, lipid oxidation can promote the degradation of drugs sensitive to oxidative decomposition, like vitamins.

The main objective of this work was to study the oxidative resistance of the two types of semi-solid oily formulations for hard gelatin capsules filling and to confirm the negative effect of their oxidation on the stability of vitamin A, used as model substance.

Given that most pharmaceutical products with a high oil content go rancid rather slowly under normal conditions of conservation, the evaluation of their stability in a reasonable time requires certain factors such as heat and the passage of air or oxygen, which speed up oxidation. In the first phase, therefore, an accelerated oxygen model was employed in order to determine the influence of the formulation's components on the oxidative deterioration of corn oil. The technique chosen was Rancimat, which allows continuous follow-up of the oxidation.

In the second phase, vitamin A palmitate was used as model compound: the resistance to oxidation of the encapsulated vitaminic formulations was studied under storage at various temperatures. The capsules were kept at different temperatures for periods of 3, 6 and 12 months after preparation. The mean vitamin A palmitate content of the capsules was then determined by HPLC analysis; the effect of including a mixture of antioxidants (BHA + BHT) in the formulations was also evaluated. The solution of vitamin A palmitate kept under refrigeration in a nitrogen atmosphere was used as the standard and for study reference at 30°C the same solution kept at that temperature.

	initiator		O_2		RH			O_2	
Unsaturated fatty acids	→	Radical ($R^{\cdot}$)	→	Peroxide ($ROO^{\cdot}$)	→	Hydroperoxides (ROOH)	→		Secondary oxidation products

Table 1
Composition of semi-solid formulations

Composition (%)	A	A-vit	A-vit + BHA/BHT	B	B-vit	B-vit + BHA/BHT
Vitamin A palmitate	—	10	10	—	10	10
Corn oil	60	45	45	35	25	25
Imwitor 900®	10	15	15	—	—	—
Cremophor RH 60®	30	30	30	15	15	15
Brij 58®	—	—	—	15	15	15
PEG 400	—	—	—	35	35	35
BHA	—	—	0.05	—	—	0.05
BHT	—	—	0.05	—	—	0.05

2. Materials and methods

2.1. Materials

Products used in the preparation of the different semi-solid bases for later encapsulation were: corn oil (pharmaceutical quality), glyceryl monostearate (Imwitor 900®, HÜLS), polyoxyl 60 polyoxyethylenated castor oil (Cremophor RH 60®, BASF), polyoxyethylene 20 cetyl ether (Brij 58®, ICI-Atlas) added with 0.01% butylated hydroxyanisol (BHA) and 0.005% citric acid as antioxidants, polyethylene glycol 400, BHA, and butylated hydroxytoluene (BHT) (pharmacopoeia quality).

Pharmacopoeia quality retinol palmitate (distributor: Igoda, Prod. Quim.) was used. It is an oily concentrate of vitamin A palmitate dissolved in peanut oil and stabilized with BHA/BHT (1 g = 1 000 000 IU).

2.2. Formulations studied and method of preparation

Two series of formulations with vitamin A (formulations A-vit and B-vit) were prepared, with and without antioxidants, derived from two stable excipient mixtures referenced in the bibliography: formulae A and B of Table 1. The first of these excipient mixtures was a semi-solid-lipid matrix (Kinget and De Greef, 1994), while the other was a self emulsifying system (Halbaut et al., 1995b, 1996).

Small quantities of the mixtures were prepared under rigorously standardized conditions in order to standardize their thermal history. The components of the mixture were fused at 10°C above the melting point of the excipient with the highest melting point. They were then cooled to the ambient temperature in a water bath at 19°C under constant mechanical agitation.

The antioxidants were added at the beginning of the process before the components were fused; the vitamin A palmitate was added during the cooling phase, when the mixture reached approximately 40°C.

The capsules were filled manually with a plunger, placing 250 mg (± 1%) in Elanco Qualicap capsules, Posilok model, transparent No. 2. The medicaments contained 10% active compound giving a theoretical vitamin A dose per capsule of 25 000 I.U.

The capsules were kept in transparent glass phials, hermetically sealed and shielded from light.

2.3. Resistance to oxidation: the Rancimat method

Of the various techniques proposed for the determination of the resistance of oils and fats to oxidation, the Rancimat method has recently been the most frequently cited. Its main advantages are its automated nature and its saving in time and reagents.

2.3.1. Measurement principles

The stability of fatty substances was determined by accelerated oxidation with a dry air flow and a high temperature (100–140°C). The volatile com-

ponents (mainly formic acid) which arose from the oxidative decomposition of the samples were drawn off and collected in twice-distilled water (mili-Q: 3–4 μS). Conductimetrical measurements were taken and conductivity was automatically recorded against time.

2.3.2. Equipment and curves obtained

Metrohm Rancimat, model 679, comprising two modules: reactor and processor. The reactor, with a capacity for six samples, allows them to be subjected simultaneously to a current of dry air and to the action of the temperature. Fig. 1 shows a diagram of one of the six reactor units. The second module is the control unit, fitted with a keyboard for entering the chosen parameters (temperature, duration of assay, cell constant etc.). It controls and evaluates the readings obtained in the reactor, which outputs its graphic display to a thermal-paper printer, integrated into the unit. Fig. 2 shows a typical profile of the graphics obtained.

The oxidation curve thus determined runs parallel to the peroxide values (Läubli and Bruttel, 1986).

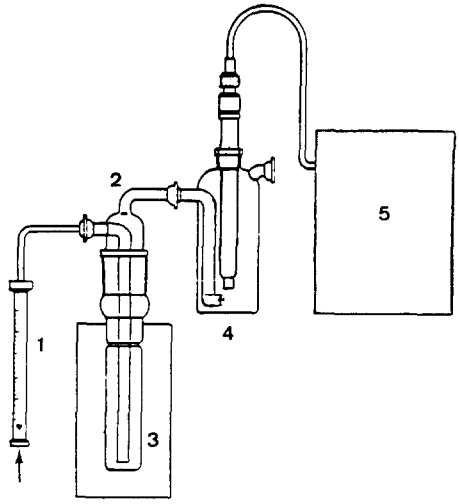

Fig. 1. Diagram of the equipment for determining the induction time with Rancimat. (1) flow gauge. (2) Reactor with sample. (3) Aluminum heating element (temperature controlled to ± 0.1°C); (4) Absorption container with conductimetrical cell submerged in distilled water. (5) Conductivity signal amplifier with six recording channels. (After Läubli and Bruttel, 1986).

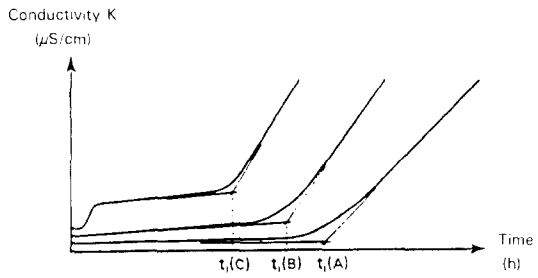

Fig. 2. Examples of graphics obtained with the Rancimat and determination of induction time t_I using the tangent method. (A) and (B), typical conductimetrical curves; (C) curve with initial jump. (After Läubli and Bruttel, 1986).

The system also permits automatic evaluation of the induction period t_I from the curve $K=f(t)$, where K is the conductivity expressed in μS/cm, and t the time in hours.

The induction time is defined as the time necessary to reach the inflection point of the curve, which is calculated from the intersection of the tangents of the curve projected over the time axis (Fig. 2). It can be correlated with the A.O.M. values and is a characteristic of oxidative stability.

2.3.3. Preparation of the sample and operating method

To submit the samples to oxidation in the Rancimat, 3.5 g of sample was placed into each reaction tube (2 tubes per sample). Accelerated oxidation was carried out at 120°C with an air flow of approximately 20 l/h. As mentioned above, an automatic graphic output of conductivity against time was obtained at the end of each oxidation assay.

2.4. HPLC determination of mean vitamin A palmitate content

In each assay the mean content of vitamin A palmitate in ten capsules was determined by HPLC. An analytical method was developed and previously validated, for this purpose, using the equipment, reagents, chromatographic conditions and protocols described below.

2.4.1. Equipment

Liquid/liquid chromatograph consisting of:

- Kontron pump (Mod. LC Pump 414)
- Automatic injector Promis Spark Holland
- Kontron variable-wavelength UV detector (Mod. Uvikon 720LC); wavelength $\lambda = 326$ nm
- Merck Hitachi chromato-integrator (Mod. D2500)

2.4.2. Reagents

- Absolute ethanol for analysis (Panreac ref. 131086)
- Chloroform (trichloromethane stabilized with ethanol; Panreac ref. 261252)
- Methanol for HPLC (Promo Chem)
- Acetonitrile for HPLC (Carlo Erba)

2.4.3. Chromatographic conditions

- Stationary phase: column C18 (Nucleosil, 5μ); dimensions 125 × 4.6
- Pressure: 150 bar (approx.). Temperature: ambient.
- Mobile phase: methanol/acetonitrile (70:30 v/v) freed of air by means of helium gas
- Isocratic flow: 3 ml/min
- Volume injected: 10 μl
- Detector at 326 nm: detector sensitivity 0.4 AUFS
- Paper speed: 5 mm/min
- Attenuation: 10

2.4.4. Experimental protocol

An aliquot (theoretical content 25 000 IU vitamin A) of the mixture of the contents of ten capsules was analyzed after their contents had been carefully removed with a small spatula: the contents were mixed and about 250 mg of product (P_{prob}) was weighed exactly in a 20 ml precipitation beaker, with a theoretical vitamin A content of 25 000 IU. To dissolve the mass, 10 ml of ethanol (for formulation B-vit) or chloroform (for formulation A-vit) was added. It was placed in an ultrasound bath to speed dissolution. The contents of the beaker were transferred quantitatively to a 50 ml measuring flask by means of successive portions of ethanol, it was levelled off, and subjected once again to ultrasound. The problem solution was analyzed in triplicate, 10 μl of it being injected each time. The chromatograph showed a peak due to vitamin A palmitate at a retention time of 6.60–7.00 min. The areas obtained were recorded (A_{prob}).

A standard solution of recently prepared vitamin A palmitate, containing a known quantity (C_{stand}) close to 50 mg and dissolved in 100 ml ethanol, had previously been triply analyzed. The mean area of the peaks obtained was determined (A_{stand}). It was shown that the excipients do not interfere in the reading zone: the base line did not change after analysis under the same conditions.

Calculation of the mean vitamin A content (IU/capsule), taking 1 000 000 IU/g as the theoretical content of the raw material:

$$\frac{A_{prob} \cdot C_{stand} \cdot 50}{A_{stand} \cdot 100 \cdot P_{prob}} \cdot P_c \cdot 1000$$

where A_{prob}: Area of problem product, A_{stand}: Mean area of standard, P_{prob}: Exact weight of sample analyzed, C_{stand}: Quantity of standard (in 100 ml), P_c: Mean weight of capsule content ($P_c = 250$ mg).

2.4.5. Validation of analytical method

In the validation of the analytical method the following points were determined: linearity, accuracy (replicability and reproducibility) and exactitude (Castro Cels et al., 1989).

(1) Linearity assay: The linearity of an analytical method is taken to mean its ability to obtain results linearly in proportion to the concentration of analyte in the sample within a determined time.

The linearity of the method was proven by preparing a primary solution with approximately 100 mg vitamin A palmitate in 100 ml ethanol. Different strengths of dilution were made with ethanol from this primary solution: 6.25, 12.5, 25, 50, and 75 mg/100 ml. Each sample, including the primary solution, was triple-analyzed and the regression line, the value of r^2 (coefficient of determination) were calculated.

A linearity test was performed by calculating the coefficient of variation of the response factors (f) (relationship between reading and concentration). These must be similar to each other and

close to the value of the slope. Values greater than 5% indicate a lack of linearity.

(2) Accuracy: Accuracy is an estimation of the variability of the measurements. It is defined as the degree of concordance between individual results obtained from a homogeneous sample; the term covers the two aspects of replicability and reproducibility.

(3) Replicability: This is defined as the measure of accuracy of a method applied to the same sample under the same conditions and after a short period of time. The replicability of the system was determined from the values obtained in the linearity assay. It was calculated by means of the following equation:

$$\text{Accuracy (CV\%)} = \frac{S}{X} \cdot 100$$

where S is the standard deviation of the samples for each concentration and X is the mean experimental concentration. In analysis of finished product coefficients of variation lower than 2–3% are considered acceptable.

(4) Reproducibility: This is defined as the measure of accuracy of a method applied to the same sample, but under different conditions. For this purpose the above linearity assay was repeated 24 h later using the same standard solutions. The mean value of the six analyses (the three obtained in the assay plus the three previous ones from the replicability assay) was determined, as was the coefficient of variation. In analysis of finished product coefficients of variations lower than 4–5% are considered acceptable.

(5) Exactitude: Exactitude represents the degree of concordance between the results obtained in the analysis and the true value. It was determined for each standard solution from the six readings obtained in the replicability and reproducibility assays. It is expressed mathematically as the difference between the value found and the real value:

$$\text{Percent relative error} = \frac{\text{Mean value} - \text{Real value}}{\text{Real value}} \cdot 100$$

Student's t-test was used to determine whether there were significant differences at a determined level of significance between the experimental value found and the theoretical value.

The experimental t was calculated from the following equation:

$$t_{exp} = \frac{|m - x| \cdot \sqrt{n}}{S} = \frac{|100 - R| \cdot \sqrt{n}}{CV}$$

m: true value, x: mean experimental value, S: standard deviation, n: number of determinations.

If $t_{exp} < t_{theor}$ for the chosen level of probability and $n - 1$ freedom degrees, the exactitude of the method can be confirmed.

2.5. Thermal stability

Recently prepared capsules were kept at (6 ± 2°C), ambient temperature (22 ± 2°C), and in a kiln at (30 ± 1°C).

The capsules were analyzed 3, 6, and 12 months after preparation to determine their physical stability as well as the stability of the active principle.

At these times 20 capsules were taken at random from each batch, they were examined to check the integrity of the gelatin container, and they were weighed after they had been carefully cleaned with absorbent paper, in order to detect possible loss of contents. The mean content of active principle was then determined using the procedure described above.

3. Results

3.1. Oxidation of corn oil

In order to determine the influence of the components of the bases on the oxidative stability of the corn oil, the resistance of corn oil to oxidation alone and mixed with the other excipients was determined. To facilitate comparison between the two types of bases under study, formula B was modified to include 25% more corn oil at the expense of PEG 400, thus making the same percentage of corn oil (60%) as in formula A, although this affected the physical stability of the preparation as has been shown previously (Halbaut et al., 1995b).

Table 2
Induction times obtained by the Rancimat method, mean values, standard deviations and coefficients of variation for corn oil and formulations A and B modified

Samples	Induction times (h)		Mean value (X)	Standard deviation (S)	Coefficient of variation (CV)
Corn oil	2.38	2.28	2.26	±0.13	5.7%
	2.28	2.38			
	2.28	2.25			
	1.97	2.22			
Formula B modified	2.40	2.48	3.39	±0.82	24.2%
	3.83	3.07			
	3.84	2.37			
	4.78	3.87			
Formula A	5.78	---	4.50	±0.77	15.4
	5.98	4.00			
	4.85	5.50			
	4.23	4.65			

The level of peroxides of corn oil had previously been determined according to regulation UNE 55023 and was 7.26.

Table 2 shows the induction time values (inflection point of the curves) with their respective mean values and standard deviations.

The corn-oil curves show a sharp inflection after a relatively short induction period of 2.26 h, which is characteristic of polyunsaturated seed oils.

The curves of the formulations A and B modified show inflections after a mean induction period of 4.50 and 3.39 h, respectively. It is consequently deduced that these formulations, each of which contains 60% corn oil, have a higher level of oxidative stability than the original corn oil alone. Thus it is clear, even allowing for the quantitative differences, that corn oil is protected from oxidation by the modified formulation B, and even more so by A. This is explained by the probable presence of antioxidants in the added products as is recognized in some cases by the commercial companies themselves (e.g., Brij 58® contains BHA and citric acid).

3.2. Capsules shell integrity and resistance to leakage

During storage, at all temperatures, the vitamin A capsules were unharmed and no loss of contents was observed. Mean weight variation did not exceed 0.4%.

3.3. HPLC analysis of vitamin A palmitate: validation of the analytical method

(1) Linearity: It was considered that under the assay conditions as described, the technique presented a true linear response for vitamin A palmitate between 0.0625 and 1.00 mg/ml, with a determination coefficient r^2 of 0.9999 and a coefficient of variation for the f factor < 4.1.

(2) Replicability: As described above with a variation coefficient less than 2%.

(3) Reproducibility: This assay produced a coefficient of variation less than 2% in all cases, which confirms the high reproducibility of the method within the time studied.

(4) Exactitude: $t_{exp} < t_{theor} = 2.57$ ($p < 0.05$; freedom degree 5), which shows that there are no significant differences between the theoretical value and the value found, and confirms the high exactitude of the method.

3.4. Vitamin A content: effects of temperature and storage time

Table 3 shows the initial vitamin A content of capsule batches A-vit and B-vit, and the values

Table 3
Mean vitamin A content in recently prepared capsules and at 3, 6, and 12 months under refrigeration, at ambient temperature, and at 30°C

Time	A-vit (UI)			B-vit (UI)		
	6°C	22°C	30°C	6°C	22°C	30°C
t_0	25 572 ± 95	25 572 ± 95	25 572 ± 95	25 870 ± 246	25 870 ± 246	25 870 ± 246
3 months	25 163 ± 312	24 956 ± 404	21 268 ± 362	25 655 ± 493	25 842 ± 436	21 756 ± 1038
6 months	24 283 ± 383	20 898 ± 290	16 399 ± 132	25 032 ± 136	22 697 ± 320	16 974 ± 275
12 months	22 810 ± 330	8123 ± 105	2663 ± 59	24 020 ± 329	15 284 ± 294	5186 ± 108

obtained during their storage in a refrigerator, at ambient temperature, and at 30°C. Percentages calculated against time are shown in Figs. 3 and 4.

Table 4 shows the content of the same formulations stabilized with two antioxidants (0.05% BHA and 0.05% BHT), shortly after preparation and during storage at 30°C. For reference the values obtained for vitamin A palmitate alone, stored under the same conditions, are also shown. The percentages calculated against time are shown in Fig. 5.

It can be seen that initially the different batches of capsules conform to the regulations laid down by USP XXIII/NFVIII with regard to vitamin A content, the mean lying between 23 750 and 30 000 IU.

However, during storage a diminution in mean vitamin A content was observed in both formulations: the higher the temperature, the greater the loss. This degradation is in fact completely predictable, since vitamin A is sensitive to temperature and oxidation (DeRitter, 1982). In the formulations kept at 30°C the loss of content was considerable, reaching 10.5 and 20.0% for formulations A-vit and B-vit respectively (Figs. 3 and 4). At ambient temperature both formulations remained stable for 3 months, after which time there was a rapid diminution of content. Only formula B-vit, encapsulated and kept under refrigeration for 12 months remained stable within the limits laid down by the pharmacopoeia.

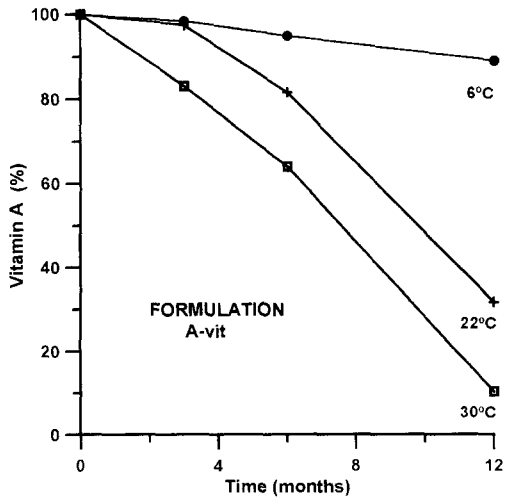

Fig. 3. Vitamin A content of encapsulated formulation A-vit against temperature and storage time.

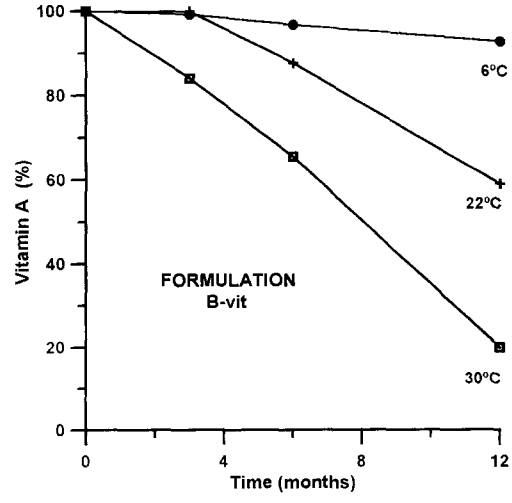

Fig. 4. Vitamin A content of encapsulated formulation B-vit against temperature and storage time.

Table 4
Mean vitamin A content in recently prepared capsules and at 3, 6, and 12 months under refrigeration, at ambient temperature, and at 30°C

Time	A-vit + BHA/BHT (IU)	Vitamin A palmitate (IU)	B-vit + BHA/BHT (IU)
t_0	25 544 ± 214	25 041 ± 41	25 766 ± 224
3 months	23 865 ± 201	23 335 ± 436	24 367 ± 139
6 months	21 264 ± 289	19 683 ± 237	22 510 ± 73
12 months	17 401 ± 277	13 630 ± 323	19 739 ± 199

4. Discussion and conclusion

It can be deduced from the results displayed in Tables 1 and 3, and Table 4, and in Fig. 5, that vitamin A without a vehicle degrades less than when base A-vit or B-vit (without antioxidants) is added. This can be attributed to the corn oil in the capsules, which is very sensitive to oxidative degradation, even though the bases in the study appear to protect the oil from oxidative degradation (see Section 3.1).

Comparison of the stability results of both formulations without added antioxidants shows greater vitamin A loss in formula A-vit (45% corn oil) than in formula B-vit (25%). (Figs. 3 and 4, and Table 1.)

Furthermore, Fig. 5 clearly shows the protective effect of adding 0.05% BHA and 0.05% BHT to both formulations. With antioxidants they had a 1-year vitamin A content of 68.0 (A-vit) and 76.6% (B-vit).

Although the addition of the BHA/BHT mixture in the proportions indicated improves the stability of the preparation against oxidation, this is not enough to stabilize the vitamin A, which probably acts itself as an antioxidant in the overall formula, partially preventing the oxidation of the corn oil.

Thus, a determining factor in the preformulation of semi-solid mixtures with vegetable oil for oral use is the necessary control of the systems stability against oxidation.

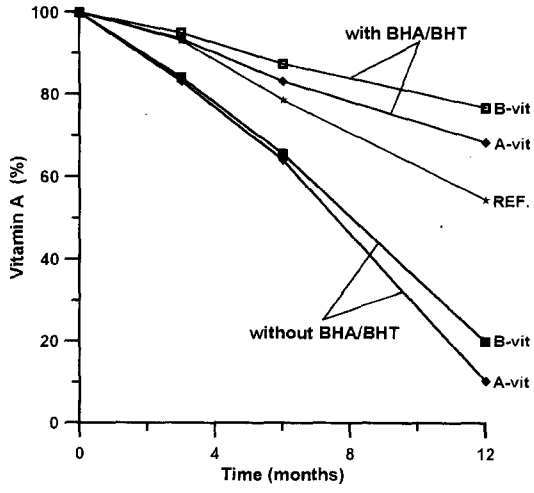

Fig. 5. Vitamin A content of encapsulated formulae A-vit and B-vit, with and without added antioxidants, as well as of the vitamin alone, against time and storage at 30°C.

References

Augsburger, L.L., Hard and Soft Gelatin Capsules. In Banker G.S. and Rhodes C.T. (Eds.), *Modern Pharmaceutics*, 2nd ed, Marcel Dekker, New York, 1990, pp. 442–490.

Castro Cels, M., Gascón Fora, S., Pujol Forn, M. et al., Validación de métodos analíticos: *Monografía Asociación Española de Farmacéuticos de la Industria* (A.E.F.I.) (1989) 94.

DeRitter, E., Vitamins in pharmaceutical formulations. *J. Pharm. Sci.*, 71 (1982) 1073–1096.

Frankel, E.N., Natural and biological antioxidant in food and biological systems. Their mechanism of action, application and implications. *Lipid Technol.*, 7 (1995) 77–80.

Halbaut, L., Barbé, C. and del Pozo, A., Bases semisólidas para el llenado de cápsulas de gelatina dura (III): Mezclas con aceites. *Cienc. Pharm.*, 5 (1995a) 59–72.

Halbaut, L., Barbé, C. and del Pozo, A., Bases semi-solides destinées au remplissage de gélules contenant du PEG 400 et une huile végétale. Caractérisation physico-chimique. *S.T.P. Pharma Sci.* 5 (1995b) 208–215.

Halbaut, L., Barbé, C. and del Pozo, A., An investigation into physical and chemical properties of semi-solid self-emulsifying systems for hard gelatin capsules. *Int. J. Pharm.*, 130 (1996) 203–212.

Kinget, R. and De Greef, H., Absorption characteristics of novel 8-MOP semi-solid-lipid-matrix formulations: In vitro-in vivo correlation. *Int. J. Pharm.*, 110 (1994) 65–73.

Kinget, R. and Van Roelen, R., The absorption of 8-methoxypsoralen from lipid-containing semisolid matrices for oral use: a prospective study in rabbits. *J. Dermatol. Treat.*, 5 (1994) 25–28.

Läubli, M.W. and Bruttel, A.P., Determination of oxidative stability of fats and oils: Comparison between the active Oxygen Method (AOCS Cd 12–57) and the Rancimat Method. *J. Am. Oil Chem. Soc.*, 63 (1986) 792–795.