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RESEARCH ARTICLE

Physical stability and resistance to peroxidation of a range of liquid-fill hard gelatin capsule products on extreme long-term storage

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Abstract

Background: The industrial take-up of liquid-fill hard capsule technology is limited in part by lack of published long-term physical and chemical stability data which demonstrate the robustness of the system.

Objective: To assess the effects of extreme long-term storage on liquid-fill capsule product quality and integrity, with respect to both the capsules *per se* and a standard blister-pack type (foil–film blister).

Materials and methods: Fourteen sets of stored peroxidation-sensitive liquid-fill hard gelatin capsule product samples, originating ~20 years from the current study, were examined with respect to physical and selected chemical properties, together with microbiological evaluation.

Results and discussion: All sets retained physical integrity of capsules and blister-packs. Capsules were free of leaks, gelatin cross-linking, and microbiological growth. Eight samples met a limit (anisidine value, 20) commonly used as an index of peroxidation for lipid-based products with shelf lives of 2–3 years. Foil–film blister-packs using PVC or PVC–PVdC as the thermoforming film were well-suited packaging components for the liquid-fill capsule format.

Conclusion: The study confirms the long-term physical robustness of the liquid-fill hard capsule format, together with its manufacturing and banding processes. It also indicates that various peroxidation-sensitive products using the capsule format may be maintained satisfactorily over very prolonged storage periods.

Keywords: Long-term; disintegration; cross-linking; leak; blister; microbiological; lipid; pharmaceutical; nutraceutical

Introduction

Liquid-fill hard gelatin capsule technology is used for a number of commercial products using both thermosoftening and liquid formulations (Rowley, 2004; Bowtle, 2007; Cole, 2007). In practice, its use by industry for the latter has been restricted by concerns on stability issues and incidence of leaks, together with lack of published experience. This article refers to examination of a range of size-zero gelatin liquid-fill capsules that had been manufactured at 20 ± 2°C under nitrogen in a GMP facility on commercial-scale liquid-fill and sealing equipment (Bosch 1500L/Qualicaps S-100), assembled into cartoned blister-packs (Bosch 1560 TLT) and stored under ambient conditions for *circa* 20 years. They were suited to assessment of capsule long-term integrity since there was substantial information on their original manufacture and had been under the direct control of one of the authors since their preparation. The samples consisted of a range of nutraceutical oils whose physical and chemical characteristics presented physical and stability challenges for liquid-fill hard capsule products. As glyceride oils, they represented models of lipid carriers that may be used in formulation development and commercial manufacture of liquid-fill capsules. Six products originated as demonstration samples from pre-production activities used to work up processes and documentation

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in 1989. Eight products originated from a stability-test series established in 1990 and terminated for nontechnical reasons at 6 months. The latter set was supported by contemporary batch processing and testing documentation. The sample sets provided a unique opportunity to assess quality-related factors for liquid-fill hard capsules with respect to long-term integrity of the capsule shell (appearance, leaks, embrittlement, cross-linking) and contents (organoleptic properties, peroxidation status), along with the microbiological status of the stored products. The study also examined blister-pack integrity and assessed the influence of pack components on product stability.

Materials, data sources and methods

Materials and data sources

Tables 1 and 2 define products and product components, respectively. The input raw materials and pack components were purchased as contemporary industry-standard materials from European industry-standard suppliers and were certified to meet the relevant specifications, including assay and peroxide values (PVs). Products containing cod liver oil were made to contain enhanced levels of vitamins A and D. All other materials were used as supplied. Each was the subject of identification before use. Capsule fill weight was standardized at 505 mg. Originating data for the pre-production samples (series "**A** x") were limited and assembled here from miscellaneous contemporary records. Data on originating raw materials and test results for the stability-test samples (series "**ST** xyz") are cited from archived original batch documents (processing/packaging/contemporary analytical test results/materials batch references). Stability-test samples were prepared under the standardized manufacturing conditions defined by the pre-production trials, with appropriate full (archived) manufacturing and assembly documentation. Their batch sizes were 9000–11,000 capsules. Pre-production samples were tested for leaks by visual examination after overnight placement on indicator paper. Stability-series samples were stress-tested for leaks using an in-house standard test (vacuum challenge, 25 mm Hg/20 min). Samples were assembled into blisters and cartons (three blisters of 10 capsules each per pack). Each blister was embossed with the relevant batch identifier. Stability-test samples were monitored for a few months with respect to physical properties and oxidation status. The test samples were thereafter kept under ambient conditions until December 2009, when they were re-examined in the current study, this effectively being some 20 years ± 3 months after their manufacture and assembly. There was no intervening controlled storage in the period, with the samples having been the subject of periodic handling and movement, including transport.

Methods (current testing)

The various samples were the subject of current examination according to a standard protocol established for this exercise to investigate major quality parameters (blister-pack integrity, capsule shell integrity, contents integrity, and microbiological status). The protocol accounted for restricted sample availability which precluded statistical sampling or evaluation. Chemical testing was restricted to assessment of peroxidation of contents, as an index of chemical stability. Direct product assays were outside the scope of this study. For the purposes of comparison, the protocol provided for scaled reporting of relevant parameters (e.g. 0 = "normal" and 5 = "gross/unacceptable"). The product characteristics that were identified as indices of change with time were as listed in Table 3.

Initial capsule appearance was examined *in situ* in blister-pockets. Pack components were examined visually and by manipulation. Blister-pack seal integrity testing was an in-house method (single blister-strip immersed in a dye solution for 50 sec at 15 mm Hg). Capsules were removed and examined for physical and organoleptic (color, odor) characteristics and microbiological status. Shell flexibility was assessed by manipulation (five capsules per set). Seal integrity evaluation

Table 1. Products and month/year of manufacture.

Sample set	Product	Month/year of manufacture
A1	Salmon oil, 500 mg (Salmon)	9/1989
A2	Cereal germ oil, 500 mg plus vitamin E (CGO–vit E)	9/1989
A3	Evening primrose oil, 500 mg (EPO)	9/1989
A4	Borage oil, 500 mg (BOR)	9/1989
A5	Safflower oil, refined, 500 mg (SAF)	9/1989
A6	Cold-pressed wheat-germ oil, 500 mg (WGO)	9/1989
ST 2A	Cod liver oil (2500 IU vitamin A, 100 IU vitamin D) (CLO)	3/1990
ST 5B	Evening primrose oil, stabilized, 500 mg (EPO)	3/1990
ST 13A	D-alpha Tocopherol acetate (200 IU vitamin E, natural source) in safflower oil, refined (TOCNAT–SAF)	3/1990
ST 19 A	DL-alpha Tocopherol acetate (200 IU vitamin E) in cold-pressed wheat-germ oil (TOC–WGO)	3/1990
ST 20A	DL-alpha Tocopherol acetate (200 IU vitamin E) in safflower oil, refined (TOC–SAF)	3/1990
ST 22B	Cod liver oil (2500 IU vitamin A, 100 IU vitamin D) (CLO)	4/1990
ST 23A	Evening primrose oil, refined, stabilized, 250 mg/borage oil, refined 250 mg, shell 2 (EPO–BOR)	5/1990
ST 24A	Evening primrose oil, refined, stabilized, 250 mg/borage oil, refined, 250 mg, shell 1 (EPO–BOR)	5/1990

Table 2. Components and supplier listing.

Component (supplier)	Sample set													
	A1	A2	A3	A4	A5	A6	ST 2A	ST 5B	ST 13A	ST 19A	ST 20A	ST 22B	ST 23A	ST 24A
Gelatin capsule, size 0, "Posilok," transparent/clear, (Shell "1") (a)	+	+	+	+	+	+	+	+	+	+	+	+		+
Gelatin capsule, size 0, "Licap," transparent/clear, (Shell "2") (b)													+	
Cod liver oil (c)							+					+		
Vitamin A palmitate, 1.7 M IU/g (d)							+					+		
Vitamin D, oily, 1.0 M IU/g (d)							+					+		
D-alpha Tocopherol acetate (natural source), 1250 IU/g (e)									+					
DL-alpha Tocopherol acetate, 1100 IU/g (f)										+	+			
Safflower oil, refined (g)									+		+			
Evening primrose oil, refined (ascorbyl palmitate and DL-alpha tocopherol) (d)								+						
Evening primrose oil, refined (ascorbyl palmitate and DL-alpha tocopherol) (d)													+	+
Borage oil, refined (d)													+	+
Salmon oil (h)	+													
Cereal germ oil + vitamin E (h)		+												
Evening primrose oil (h)			+											
Borage oil (h)				+										
Safflower oil, refined (h)					+									
Cold-pressed wheat-germ oil (g)						+				+				
Nitrogen-gassed	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Aluminium hard-tempered foil, 20 μm (i)	+	+	+	+	+	+	+	+	+	+	+			
Aluminium hard-tempered foil, 20 μm (j)												+	+	+
PVC film, 300 μm (k)	+	+	+	+	+	+	+		+	+	+		+	+
PVC–PVdC film, 250 μm/50 g/cm² (l)								+				+		

Key to supplier: (a) Elanco Qualicaps, Basingstoke, UK; (b) Capsugel, Pontyprydd, UK; (c) Seven Seas, Hull, UK; (d) Roche, Welwyn Garden City, UK; (e) Henkel, Cork, Republic of Ireland; (f) Eisai, Hatfield, UK; (g) Alembic Products, Chester, UK; (h) not defined; (i) G&A Printers, Sittingbourne, UK; (j) Star Aluminium, Bridgnorth; UK, (k) Plastic Products Ltd., Deeside, UK; (l) DRG Flexible Packaging, Bristol, UK.

applied a manual "twist test" (five capsules per set) and the in-house stress-leak test (10 capsules per set). Capsules examined in these individual tests were used for that test only, to avoid possible impact of a test's being affected by the previous procedure. Leak testing was considered the priority test subject and was allocated the larger 10-capsule sample size, accounting for limited sample availability. The stress-leak test applies a classification system analogous to that used by capsule shell manufacturers for classification of empty capsule defects (critical/major/minor). Disintegration testing was carried out according to Ph. Eur. Method 2.9.1 using Copley ZT54 apparatus, with sinkers (six capsules per test). Anisidine value (AnV) testing of capsule contents was carried out in duplicate on single capsules, using Ph. Eur. Method 2.5.36. Spectrometry was carried out on a Unicam UV2-400 instrument. Visible-range spectra of capsule contents were determined in 1 cm cells. Spectra for the stability-test series were compared with originating data to establish changes (if any) in spectral profiles. For the purposes of current reporting, average absorbance data at 425, 475, and 500 nm are listed here. These wavelengths were selected since they were considered suited to comparisons across the sample series. Microbiological testing, aimed at determination of mesophiles, was carried out on entire single capsules of each product. Each sample was transferred from the blister-pocket directly into a sterile sample container. Growth was monitored in tryptone–soya agar (3-day incubation at 30°C) and Sabouraud–dextrose agar (5-day incubation at 22°C).

Results and discussion

Product examination

This report comments on product aging and on the suitability of the use of liquid-filling hard capsules for nutraceutical oils and lipid-based products, including examples where the material is known to be the subject of oxidation-induced degradation. The study recognized that its current test components and methods differed from those in the originating exercises, which did not envisage evaluation at an extreme time point. Nevertheless, the unusual age and condition of the samples warranted comment, since they presented a unique opportunity in evaluating the stored products against current standards. The numbers of capsules available here were inevitably small and limited the test scope. For example, there were too few samples to make any statistical observations. Clearly, samples of *circa* 20 years age would be expected to show some degree of change, varying from those representing minor technical observations, which would not be significant to the end-user, to those representing non-acceptability. Product degradation to varying degrees may be exhibited, *inter alia*, by pack failure, capsule shell change or by contents change. The criteria for continuing acceptability of specific properties were (a) product appearance similar to that expected at normal shelf life, (b) compliance with relevant industry standards (e.g. disintegration times, AnV limits), (c) maintenance of organoleptic properties likely to be acceptable to end-users, (d) freedom from capsule leaks before and after de-blistering, and (e) absence of microbiological growth.

Product appearance and blister-pack integrity

Figures 1 and 2 show photographs of blister-packs of pre-production samples (20 years and 3 months old) and stability-test samples (19 years and 9 months old), respectively. All samples matched standard requirements for product appearance, including freedom from distortion of blisters and capsules. Table 4 lists test results on evaluation of foil–film blisters. All blister-packs retained integrity, as shown by maintenance of (1) color and flexibility of lidding-foil and film and (2) non-leakage of blister-pockets under vacuum test.

Capsule shell integrity

Table 5 lists test results on evaluation of capsule shell integrity. All capsules shells maintained color, transparency and shape. They were free of adhesion. Certain results obtained on early storage at elevated conditions

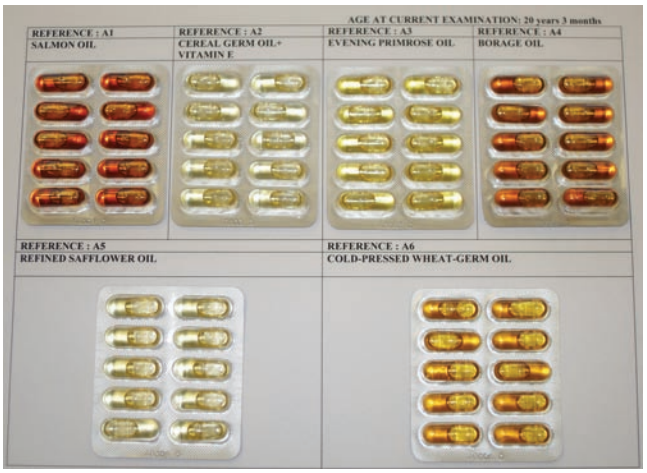

Figure 1. Photographed stored capsules (pre-production).

Table 3. Indices of product change.

Change	Component	Index of change
Physical	Blister	Film flexibility, brittleness, color, and opacity; foil flexibility and color; loss of film–foil adhesion
	Capsule shell	Deformation, flexibility, brittleness, opacity, leakage, gross capsule weight
	Content	Instrumental spectrum, organoleptic properties
Chemical	Capsule shell	Disintegration time, as an index of gelatin cross-linking, limit = 15 min
	Content	Anisidine value (AnV), as an index of oxidation, limit = 20

(not reported in detail here) had suggested a potential for later embrittlement. In practice, one sample set (*viz* safflower oil) showed embrittlement while all others maintained flexibility. The degree of embrittlement was observable in the laboratory but was unlikely to have been observed by an end-user. More importantly, it was insufficient to cause capsule damage on manual removal from the blister-pocket. The current data (20-year "real time") suggest that early accelerated stability trials overestimated likely product change. Determination of gross weights across the full sample series showed the average weight to be 605 mg (standard deviation 3.2 mg), matching the originating nominal weights for shell, fill and band of 95, 505, and 3 mg, respectively. This indicated that there was no moisture uptake or loss by the shell or contents.

A perceived major potential issue for liquid-fill hard capsules is their possible leakage that may arise through failure of the capsule seal (manufacturing failure) or through development of cracks (manufacturing failure or formulation issue). In addition, there may be concern on capsule bursting at the point of removal from a blister-pack by the end-user. Here, leaks were assessed by preliminary visual observation (before and after de-blistering) and by a vacuum-stress test: incidence and severity of leaks were determined in 10 capsules per set. The severity of any leak was classified according to an in-house standard description analogous to that used by empty capsule suppliers to classify defects (critical, major and minor). No within-blister sample showed leakage. All capsules were intact on removal from the blister-pockets. All tested samples passed the "twist test," which stressed the band security and also crack propagation. Capsules containing safflower oil showed significant hardening. Other capsules showed no or marginal loss of flexibility. None burst under manual pressure. One capsule (set ST 23A) showed a critical leak under the vacuum-stress test (10 capsules per set) that is designed to predict *future* leakage of bulk capsules and support shelf-life statements. This test represents a major challenge to capsule shell integrity. The single failure found here in 140 × 20-year-old samples, which had undergone original blister-packing, storage and de-blistering, together with the associated integrity tests described here, clearly demonstrates the reliability of the so-called band-seal process. The samples examined here are restricted to oily materials, which this study has shown to be compatible with the gelatin shell. It is recognized that other product formulations need to be evaluated for such compatibility on a case-by-case basis, using published guidelines on carrier selection (Bowtle, 2007; Cole, 2007).

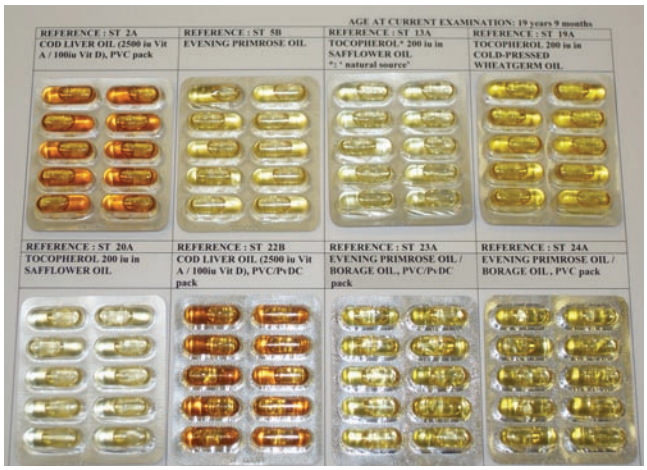

Figure 2. Photographed stored capsules (stability-test series).

Gelatin capsule shells may be the subject of aldehyde-induced cross-linking, which can result in prolonged disintegration times and which may affect product bioavailability (Brown et al., 1998). All samples had disintegration times in the range of 6–8 min, indicating that the degree of any cross-linking that may have occurred was low and insufficient to cause non-compliance with standard pharmacopoeial requirements on capsule disintegration (limit, 15 min). This is surprising in view of the nature of certain oils, especially fish oils, which would be expected to contain aldehydes but does demonstrate that stored capsules can be highly resistant to cross-linking.

Contents integrity

Table 6 lists test results on evaluation of capsule contents integrity and microbiological status.

Table 4. Test results on blister-strip integrity.

	Sample set													
Test	A1	A2	A3	A4	A5	A6	ST 2A	ST 5B	ST 13A	ST 19A	ST 20A	ST 22B	ST 23A	ST 24A
Appearance of film (test all available)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Appearance of foil (test all available)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Flexibility of film (test all available)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Integrity of blister-pocket seal (test single blister of 10 pockets)	10	10	10	10	10	10	10	(8/8)*	10	10	10	10	10	10

Key to result format: Appearance: 0 = normal, 1 = slight discoloration, 5 = gross discoloration; Flexibility: 0 = normal, 1= brittle, −1 = soft; Integrity of seal: number of non-leaking pockets in single 10-pocket blister.
*Sample availability limited to eight unopened pockets in the blister.

All capsule contents remained clear and maintained their typical product odor. Several samples, for example, fish oils and borage oil, exhibited significant color change. This was quantified for certain samples by comparison of original and current visible-range absorption spectra. The results of visible-range spectrophotometric evaluation are shown as averages of absorbance at 425, 475, and 500 nm in Figure 3.

The various oils are unsaturated lipids and therefore subject to peroxidation, which may arise from the oil *per se* or from exposure to atmospheric oxygen. It may be reduced by the presence or addition of antioxidants (Young and Bowtle, 1999) (e.g. butylated hydroxytoluene, DL-alpha tocopherol, or ascorbyl palmitate). There are two common measures of peroxidation in oils, *viz* PV and AnV. However, PVs of the triglyceride oils are known to reach a maximum and then decrease in value as the peroxides degrade into secondary oxidation products and are therefore not reliable indices of peroxidation at late time (there were limited originating data on PVs: contemporary product manufacturing specifications required the PV of filled capsules to be not more than 5 mEq/kg greater than

Table 5. Test results on capsule shell integrity.

	Sample set													
Test	A1	A2	A3	A4	A5	A6	ST 2A	ST 5B	ST 13A	ST 19A	ST 20A	ST 22B	ST 23A	ST 24A
Average gross weight, mg (test 10)	608	607	607	600	608	609	607	607	605	601	600	602	603	603
Incidence of visible leaking (test all available)	0 ex 30	0 ex 30	0 ex 29	0 ex 30	0 ex 30	0 ex 30	0 ex 10	0 ex 16	0 ex 30	0 ex 30	0 ex 20	0 ex 30	0 ex 20	0 ex 30
Shell deformation (test all available)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Shell discoloration (test all available)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bursts on de-blistering (test 10)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Shell flexibility (test 5)	1	0	0	0	0	0	0	0	4	0	0	0	0	1
Band security (test 5)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Leaks under vacuum test (test 10)	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Key to result format: Incidence of visible leaking: number examined/number leaking; Deformation: 0 = normal, 1 = slight distortion, 5 = gross distortion; Discoloration: 0 = normal, 1 = slight discoloration, 5 = gross discoloration; Bursts on removal: number, ex 10; Shell flexibility: 0 = normal, (−1 to −5) = softening, (1–4) = hardening, (−5 or 5) = bursts on pressure; Band security: 0 = normal, 1 = breaks or bursts; Leaks under vacuum: number leaking.

Table 6. Test results on capsule contents integrity and microbiological evaluation.

	Sample set													
Test	A1	A2	A3	A4	A5	A6	ST 2A	ST 5B	ST 13A	ST 19A	ST 20A	ST 22B	ST 23A	ST 24A
Color (current/original)	5/†	1/†	2/†	5/†	1/†	4/†	4/2	2/2	2/1	3/2	1/1	4/1	2/1	2/1
Clarity	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Odor	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Microbiological monitor	0	0	0	0	0	0	0	0	0	0	1*	0	0	0

Key to result format: Color: 1= very pale yellow, 5 = deep golden brown; Clarity: 1 = clear, 5 = highly clouded; Odor: 1 = typical for fresh oil, 5 = rancid; Microbiological monitor: 0 = no growth; 1 = growth.
*(Two colonies) of *Micrococcus* sp., considered to have arisen during the sampling of the capsules.
†No data available.

the input material). The related anisidine test is not the subject of this limitation since it refers to secondary oxidation. Limited sample availability precluded parallel PV and AnV testing and the latter was used here as the better index of peroxidation for these aged samples. The results of testing are shown in Figure 4. Commonly, an AnV of 20 is regarded as the limit for nutraceutical oils (2- or 3-year shelf life). Here, various samples of plant oils and vitamin

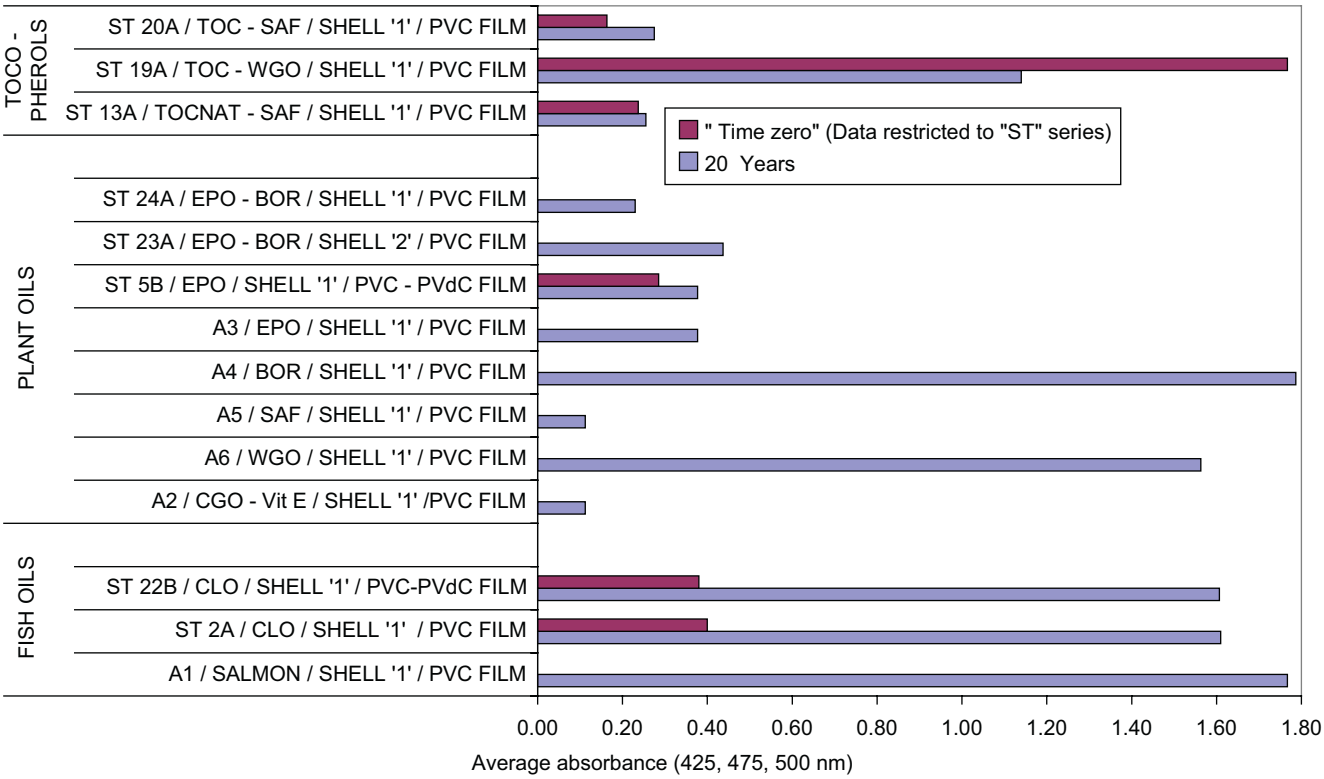

Figure 3. Average absorbance (425, 475, and 500 nm) for "time zero" and stored capsules.

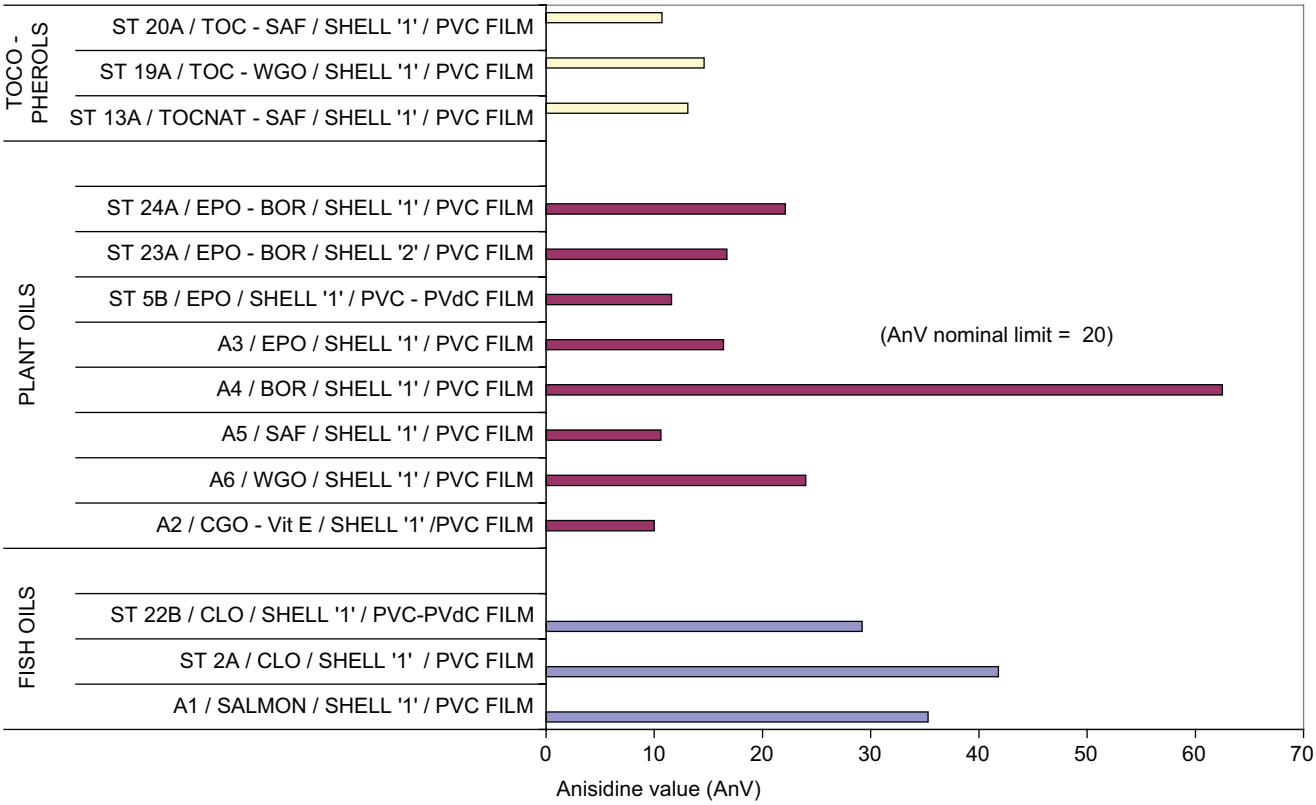

Figure 4. Anisidine values (AnVs) for stored capsules.

E met the criterion at 20-year storage. Fish oils are highly vulnerable to peroxidation and rancidification and the current samples showed AnVs of 29–42. Surprisingly, the highest value (62.5) was obtained with (unstabilized) Borage oil samples. The cause of this relatively high deterioration is unknown and could be associated with the originating plant-oil quality or the high GLA content of borage in comparison with evening primrose oil. The overall data set, however, comprises low AnVs and demonstrates low oxygen permeability of the hard gelatin shell.

The degree of secondary oxidation occurring in such oils is known to be related to color darkening. In practice, various samples darkened significantly, for example, fish oils, whereas others exhibited minor change only. No relationship could be determined between individual or averaged absorbance values at the selected wavelengths (425, 475, and 500 nm) and AnVs.

The capsules were the subject of nitrogen flushing at the time of capsule manufacture. This simple practice has been widely adopted for oxidation-sensitive products. It is aimed at minimizing oxidation due to oxygen in the headspace of the closed capsule at the time of filling and is a supportive measure only. It should not be regarded as a mechanism for eliminating oxidation of the capsule contents.

Influence of pack components on product stability

All blister-packed samples were protected from light by cartoning. In addition to mechanical protection and separation of individual dosage unit, the blister-pack format provides an impermeable aluminium base, with oxygen and water vapor transmission being controlled by the properties of the particular thermoforming film used (here, PVC and PVC–PVdC). PVC film itself has low water vapor and oxygen transmission rates, with these being reduced typically by factors of 5–10 (water vapor) and 10–25 (oxygen) on coating with PVdC ("PVC–PVdC" film). Here, capsule shell integrity in all samples suggests that moisture vapor transmission was not an issue for either pack type. The known low oxygen permeability of sealed hard capsules (Shah and Augsburger, 1989) is likely to be more important to limiting product oxidation than the nominal low oxygen transmission rate of the PVC–PVdC film, with its being recognized, however, that the AnV obtained with Set ST 22B (PVC–PVdC pack) was lower than that obtained with its pack comparator ST 2A (PVC pack).

Microbiological integrity

Visual observation of intact capsules (shell and contents) showed no signs of microbiological growth. The microbiological monitor determined mesophilic organisms. There was no attempt to determine anaerobes since the capsules had used food or pharma-grade components and had been produced and packed in a GMP environment, precluding originating presence or process-introduction of such organisms. Microbiological testing for total viable count (including yeasts and moulds) confirmed no growth. The water activity of hard capsule shells (0.15) is insufficient to support microbiological growth. The capsule contents are nonaqueous. The only moisture available is that in the hard capsule shell (14–16%) and is insufficient to allow the growth of non-fastidious organisms. One sample (sample ST 20A) showed growth (two colonies) of *Micrococcus* sp., considered to have arisen during the sampling of the capsules that included the manual process of puncturing the blister-pack pockets and transfer of the capsules to a sterile sample bag. The occurrence demonstrated that the capsules, although showing no growth in the prior 20-year period, still maintained the physical properties that would allow the transfer of viable organisms.

Relevance to pharmaceuticals

The storage period for these samples is greatly in excess of common regulatory requirements for pharmaceuticals (2–5 years). The findings, nevertheless, are of technical manufacturing and academic interest since they represent unique long-term data on the integrity of this capsule format. In particular, they address a perceived issue of the long-term vulnerability of liquid-fill hard capsules to shell and seal failure and demonstrate that the format is physically robust. They are also relevant to long-term content quality not only of the specific materials used here but also to lipid-based pharmaceuticals. The various materials examined here included long-chain unsaturated glycerides that are subject to oxidation or light-induced degradation (all samples reported here had been maintained in cartons and were therefore protected from light). They represent materials at high risk of product degradation. Certain common oily lipid carriers for liquid-fill capsules (e.g. soybean, corn, sesame, and canola) comprise long-chain unsaturated glycerides that are significant to lymphatic transport and drug absorption and require protection from oxidation and light (Bowtle, 2007). This study, using analogous materials, shows that the gelatin hard capsule format provides high protection from oxidation. The current findings show that the liquid-fill gelatin capsule is highly suited to provide a robust, physically stable, and oxidation-resistant product format for formulations using such lipid carriers. The findings support the possibility of giving much longer shelf lives to various products (e.g. liquid-fill placebos and nutraceuticals) than the current common 2- to 3-year limit.

The authors noted that it was not possible to conduct and report on stability-indicating assays on the various products within the confines of this study. Such an exercise, however, may be the subject of further work and publication.

Conclusions

Examination of a range of 20-year-old blister-packed liquid-fill banded hard capsules has demonstrated their remarkable physical stability, with specific reference to integrity of pack and capsule shell, together with freedom

from leakage and compliance with pharmacopoeial disintegration requirements. Limited chemical assessment showed various oxidation-sensitive plant-oil and vitamin E products complied with the common (AnV) index of acceptability on oxidation status, even at 20-year storage. The study confirms the long-term physical robustness of the liquid-fill hard capsule format, together with the manufacturing and banding processes. It also indicates that various oxidation-sensitive products may be maintained satisfactorily over very prolonged storage periods.

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Declaration of interest

The authors report no declarations of interest.

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