CUSTOMER SERVICE REPORT
CS0084

Technical Documentation
FM140

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Edition 2, October 2009

**** The information in this report has been prepared with utmost care and, to the best of our knowledge, contains accurate information. However, the validity of this information and its application in any specific commercial or other case is subject to confirmation by Datwyler in a formal contract. ****

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2. Description

FM140 is Datwyler's standard chlorobutyl compound with silicate filler and inorganic coloring system, using an unconventional curing system. The low number and the high-purity of ingredients translate in a low extractables/leachables profile. FM140 can be seen as a universal rubber compound used in a wide pharmaceutical application range: infusion, injection and lyophilization.

FM140 is free from natural rubber or natural rubber latex, from nitrosamines and from 2-mercaptobenzothiazole (MCBT). In addition, it complies with all major pharmacopeia for pharmaceutical rubber.

Upon request, products in FM140 can be washed using a validated washing program (ISAF) using WFI. Its good particulate cleanliness and stability upon gamma irradiation makes FM140 a compound suitable for Ready-for-Sterilization and Ready-for-Use applications. In such applications the pre-treatment of rubber parts in the form of washing, siliconisation, rinsing and eventually steam sterilization are skipped by the end user.

FM140 shows very good functional properties with an excellent coring behaviour, making this compound suitable for multidose applications.

Rubber compound FM140 is filed with the FDA in a US Drug Master File (#10953) and with the Health Protection Branch in Canada (#1994-027).

Note: FM140 refers to the type of compound. The extension "/0", "/1", … refers to the colour of the said compound.
Differently coloured compounds were used for testing throughout this document. It is generally accepted that the colour is irrelevant for the properties discussed in this document.

3. Typical compound ingredients

3.1. Natural rubber latex

Compound FM140 is free from natural rubber and natural rubber latex.

3.2. TSE/BSE

Compound FM140 does not contain material of animal origin and hence is not associated with TSE/BSE risks.
(TSE = Transmissible Spongiform Encephalopathy; BSE = Bovine Spongiform Encephalopathy)

3.3. MCBT

Compound FM140 does not contain 2-mercaptobenzothiazole (MCBT, also named MBT), or any of its derivatives.

3.4. Heavy Metals

- Compound FM140 fulfils the European Community Guideline 94/62/EC for heavy metals in packaging materials.
- Compound FM140 equally is in compliance with the CONEG regulation on heavy metals in packaging components.

Both directives state that packaging components should not contain more than 100 ppm of Lead (Pb), Cadmium (Cd), Mercury (Hg) and Hexavalent Chromium (VI) (Cr). Where the regulated metals are present at levels below the values stated above, they were not intentionally added during the manufacturing process.

3.5. Nitrosamines

Compound FM140 does not contain ingredients that potentially give rise to the formation of nitrosamines.

3.6. GMO

Compound FM140 does not contain ingredients made from GMO's (Genetically Modified Organisms).

4. Shelf Life

The shelf life of rubber compound FM140, intended for use in parenteral applications, stored in the original packaging under the ambient storage conditions as described in the ISO2230, "Rubber Products – Guideline for storage", is 2 years after packing date.
In case a pre-treatment with gamma irradiation (25kGy) is applied, the recommended use is 1 year after packing date.

Hereafter, based on the indications given in the ISO2230, an additional shelf life of 5 years can be considered. Compatibility with the drug must be ascertained by the user.

5. Physical properties

The physical properties as shown in Table 1 are taken for compound FM140/0, Gray. Properties like density and ash content may differ slightly for different colours of the compound. Data per compound colour are given on the corresponding Compound Data Sheets, available as separate documents upon request.

Table 1 : Physical properties – FM140

Hardness	°Shore A	ISO 7619	46	± 5
Density	g/cm³	ISO 2781	1.323	± 0.025
Ash	%	Internal Method(s): Calc. 4h@700°C	45.5	± 2.0
Compression Set	%	ISO 815	35	max.
Tensile Strength	N/mm²	ISO 37	3	min.

6. Chemical Properties

6.1. Pharmacopeial data

6.1.1. Pharm.Eur.3.2.9./USP<381>

A revised version of USP <381> has come into force on May 1, 2009. Sample preparation, test description and the 2-tier acceptance criteria were largely harmonized with the Pharm. Eur. 3.2.9.

The table on the next page summarizes the results of FM140 chemical testing according to both the USP <381> and the European Pharmacopeia 3.2.9.

The IR-spectrum and UV-absorbance curve for this extract is given in detail in Figure 1 and Figure 2.

Functional properties according to the Pharm.Eur.3.2.9./USP<381> are described under chapter 7 on page 10.

Table 2 : Pharm.Eur.3.2.9./USP<381> data, chemical part - FM140

Characteristic		Amount tested	Units	Limit	Typical Value	
Appearance of solution	Turbidity	Sol. S	NTU	Type I: 6.0 *(*)* Type II: 18.0 *(*)*		0.6
	Colour	Sol. S		See test procedure		pass
Acidity or alkalinity		Sol. S (20 ml)	ml 0.01M HCl ml 0.01M NaOH	0.8 0.3	Blank 0.06	0.06
					EP	0.06
					USP	0.00
Absorbance		Sol. S	A_{max}220-360 nm	Type I: 0.2 Type II: 4.0		0.02
Reducing substances		Sol. S (20 ml)	ml 0.002M $KMnO_4$	Type I: 3.0 Type II: 7.0		0.4
Extractable heavy metals		Sol. S	ppm Pb^{2+}	2	EP	<2
					USP	<2
Extractable zinc		Sol. S	ppm Zn^{2+}	5.0		0.3
Ammonium		Sol. S	ppm NH_4^+	2		<2
Residue on evaporation (only for EP)		Sol. S (50 ml)	mg	Type I: 2.0 Type II: 4.0		0.2
Volatile sulphides		20 cm²	mg S^{2-}	0.02		<0.02

** By definition corresponding with reference suspensions II and III resp.*

Figure 1 : Typical IR-spectrum of a pyrolysate (4000-625cm^{-1}) – FM140

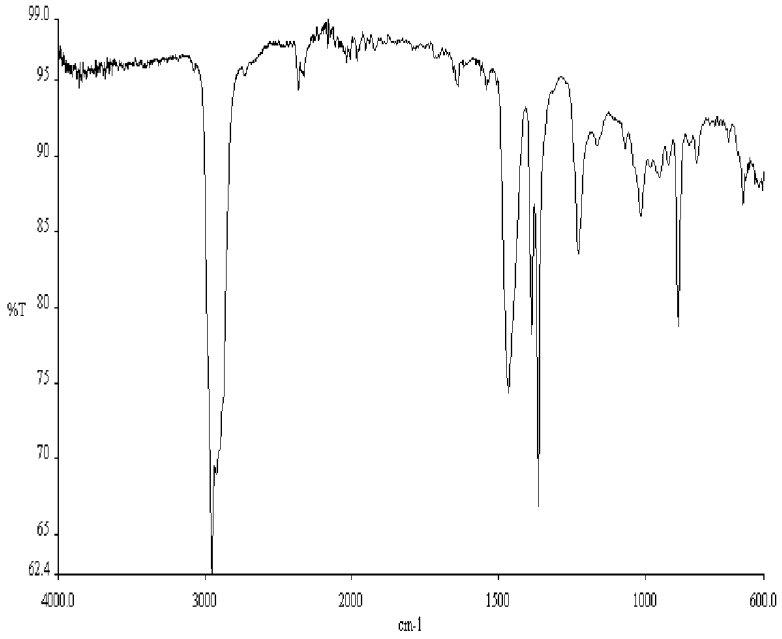
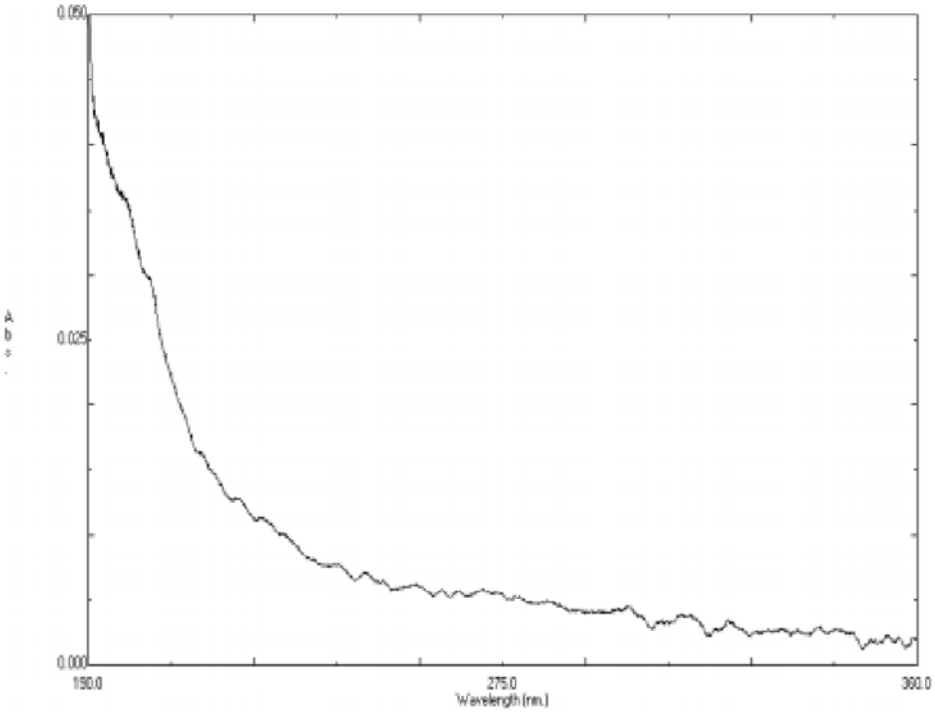


Figure 2 : Typical UV-spectrum of an aqueous extract – FM140



6.1.2. Japanese Pharmacopeia 7.03

Results for FM140/0, tested according to physicochemical part of the Japanese Pharmacopeia, chapter 7.03, “Test for Rubber Closures for Aqueous Infusions”, valid version, are given in Table 3 below. 30 g of rubber sample is autoclaved in 300 g distilled water for 60 min. at 121°).

Due to the peculiar definition of the sample preparation (by rubber mass and not by rubber surface), results are closure design dependent (surface/volume ratio dependency). Results in the table are given for the standard Datwyler 20mm injection closure V9048 (ISO8362-2) in compound FM140/0.

For the design given, FM140 complies with the extractable substances part of the Pharm. Jap. 7.03. Other parts of the Pharm. Jap. 7.03 were not tested and hence are not documented. Please contact your Datwyler sales representative in case of need.

Table 3 : JP 7.03 – FM140

CRITERIUM	AMOUNT TESTED	UNITS	LIMITS	RESULTS
Appearance (430-650 nm)	10 mm cuvet	%T at 430 nm %T at 650 nm	99% T 99% T	99.5 99.6
Foam test	5 ml	-	foam disap. < 3 min.	Pass
pH	20 ml	pH units	difference with blank: max. 1.0(*)	-0.7
Reducing substances	100 ml	ml 0.002 M $KMnO_4$	2.0	0.63
Evaporation residue	100 ml	mg	2.0	0.20
UV absorb. (220-350 nm)	10 mm cuvet	absorbance	0.2	0.03
Zinc	10 ml	ppm Zn^{2+}	1 ppm	0.67

(*) “-“ means more acidic than blank; “+” means more alkaline than blank

6.2. ISO 8871-1

The requirements of the ISO8871-1, “Elastomeric parts for parenterals and for devices for pharmaceutical use – Part 1: Extractables in aqueous autoclavates”, are identical to those set down in Pharm. Eur. 3.2.9.

Results for the Pharm. Eur. 3.2.9. are given under paragraph 6.1.1 on page 6.

7. Functional Properties

7.1. Pharm.Eur.3.2.9./USP<381>

Table 4 lists the functional properties of FM140 as per the Pharm. Eur. 3.2.9. "Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders", valid version and USP<381> "Elastomeric Closures for Injections, Physicochemical Test Procedures", valid version.
For the tests for penetrability, fragmentation and self-sealing, the same pre-treatment as described for the preparation of solution S is used (autoclaving for 30min at 121°C). Stoppers are allowed to dry.

Outline of test methods

Penetrability:
- 10 filled vials are stoppered with test stoppers and capped;
- stoppers are pierced with a 0.8 mm (21G) hypodermic needle at a controlled speed of 200 mm/min;
- the highest force is recorded;
- limit = 10 N.

Fragmentation (Coring):
- 12 filled vials are stoppered with test stoppers and capped;
- each stopper is pierced 4 times with a new 0.8 mm (21G) hypodermic needle;
- the content of 12 vials is poured over a filter;
- the number of fragments is counted by naked eye;
- limit = max. 5 fragments / 48 piercings.

Self-Sealing:
- 10 filled vials are stoppered with test stoppers and capped;
- each stopper is pierced 10 times with a new 0.8 mm (21G) hypodermic needle;
- vials are immersed upright in a 0.1% methylene blue solution;
- the external pressure is reduced with 27 kPa for 10 min;
- atmospheric pressure is reestablished and vials are left immersed for 30 min;
- vials containing any trace of coloured solution are counted;
- limit = 0 vials with coloured solution.

The results shown in Table 4 below are for a typical 20mm serum/injection stopper (ISO8362-2).

Table 4 : Pharm.Eur.3.2.9./USP<381> Functional tests – FM140

TEST	UNITS	LIMIT	TYPICAL RESULTS	STATISTICAL RESULTS (*)
Penetrability	N	10	2-3	AVG=2.67; σ = 0.316; # = 25
Fragmentation	-	5	0-1	AVG=0.20; σ = 0.41; # = 25
Self-Sealing	-	0	0	AVG=0; σ = 0; # = 25

(*) Statistical results are obtained from the Datwyler SAP computer system for the combination V9048 in FM140 (period 01/01/2007 – 31/12/2007)

The chemical properties according to this Pharm.Eur.3.2.9/USP<381> are described under chapter 6.1.1 on page 6.

7.2. ISO 8871-5

The ISO 8871-5, “Elastomeric parts for parenterals and for devices for Pharmaceutical Use – Part 5: Functional requirements and testing” describes following normative test series:

- Penetrability
- Fragmentation
- Self-Sealing
- Container Closure Seal Integrity

Annexes A, B and C, respectively for Penetrability, Fragmentation and Self-Sealing are identical to the functional testing described in the Pharm.Eur.3.2.9. Results can be found in Table 4.

Annex D, the Container Closure Seal Integrity, becomes redundant if requirements as per Self-Sealing, Annex C, are fulfilled.

8. Biological Properties

8.1. USP <1031>

The USP<1031>, “The Biocompatibility of Material used in Drug Containers”, stipulates that the biocompatibility of an elastomeric material is evaluated according to the two stage testing protocol specified in the USP<381>. An elastomeric material that does not meet the requirements of the first-stage testing (in vitro, USP<87>), may qualify as a biocompatible material by passing the second stage testing (in vivo, USP<88>).

No class or type distinction is made between elastomeric materials that meet the requirements of first-stage of testing and those that qualify as biocompatible meeting the second-stage requirements.

8.2. USP <87>

Biological testing (-elution test-) is carried out on a sample of FM140 as per the USP<87>, “Biological Reactivity Tests, In Vitro” and is proven to be non-cytotoxic. A copy of the report can be found in Figure 3 on the next page.

8.3. ISO 8871-4

The ISO 8871-4, “Elastomeric parts for parenterals and for devices for pharmaceutical use – Part 4: Biological requirements and test methods”, specifies biological requirements for bacterial endotoxins, bioburden, cytotoxicity and intracutaneous and systemic toxicity.

The requirements for endotoxins and bioburden are left open and shall be agreed upon between supplier and user.

For the toxicity tests, the same approach as in the USP<1031> is given, including reference to the USP<87>, in vitro test, for the cytotoxicity test and the USP<88>, in vivo test for the intracutaneous and systemic toxicity test.

Figure 3 : Elution test (USP<87>) – FM140

TOXIKON

225 Wildwood Ave., Woburn, MA 01801
Telephone: (617) 933-6903
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TEST RESULT CERTIFICATE

Client: Helvoet Pharma Belgium NV
Address: Industriepark, B-3570 Alken, Belgie

Technical Initiation: 04/05/94
Technical Completion: 04/07/94
Final Report: 04/07/94
P.O. #: PB944190T

Contact: Mr. Deschaetzen

Project #: 94-1301.4

TEST ARTICLE: V9046 FM140/0

LOT #: 227910

NAME OF STUDY: Elution Test

REFERENCE: This study was based on the method described in USP XXII, Pp. 1495-1497, 1990, and Supplement 9, 1993.

GENERAL PROCEDURE: The biological reactivity of a mammalian monolayer, L929 mouse fibroblast cell culture, in response to the test article was determined. The test article was extracted in cell culture medium, at a ratio of 25 cm^2 per 20 mL. Extracts were prepared at $37\pm1^{o}C$, in a humidified atmosphere containing 5±1% carbon dioxide, for 24 hours. Positive (natural rubber) and negative (silicone) control articles were prepared to verify the proper functioning of the test system. The controls were incubated similar to the test article extracts, for 48 hours. Biological reactivity (cellular degeneration and malformation) was rated on a scale from Grade 0 (No Reactivity) to Grade 4 (Severe Reactivity). The test article met the requirements of the test if none of the cultures exposed to the test article showed greater than a Mild Reactivity, Grade 2.

RESULTS: No signs of reactivity (Grade 0) were exhibited by the cell cultures exposed to the test article or the negative control article at the 48 hour observation. Severe reactivity (Grade 4) was observed for the positive control article.

CONCLUSION: The test article is considered non-cytotoxic and meets the requirements of the Elution Test, USP XXII.

AUTHORIZED PERSONNEL:

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Study Director

Katherine O'Kelly, B.S.
Quality Assurance

Environmental Sciences and Toxicology

9. Moisture content

Note: results given are only indicative as the actual moisture content is dependent on numerous factors like stopper design, packaging way, climate, etc.

Typical moisture content of rubber compound FM140 after the final treatment at Datwyler, i.e. after washing, drying and packaging, lies between 0.3-0.4 w/w% (3-4 mg_{water}/g_{rubber})

The moisture content after a steam sterilization of 30min at 121°C goes up to 1-2 w/w% (10-20 mg_{water}/g_{rubber}).

The graph below shows the impact of a typical steam sterilization on the moisture increase respectively decrease for a drying period up to 24 hours at 110 °C.

Figure 4 : Weight difference in mg/g stopper material after a steam sterilisation (30'/121°C) and subsequent drying (110°C) – FM140

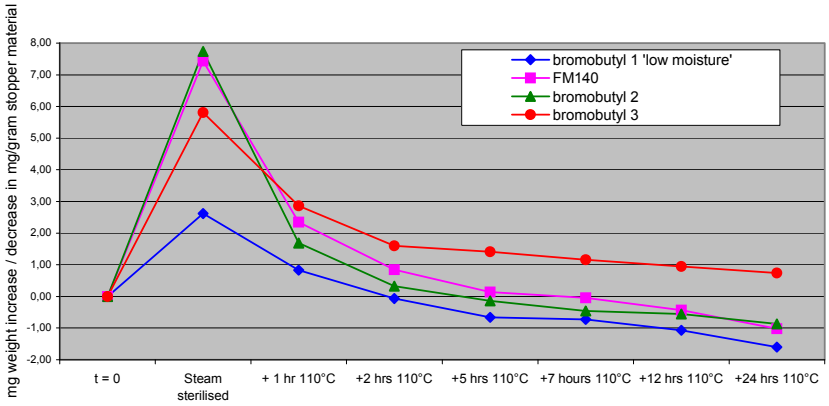
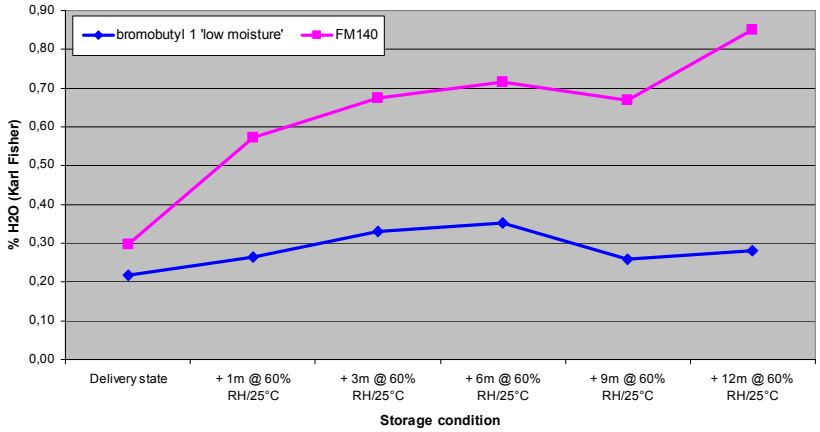


Figure 5 demonstrates the moisture uptake of rubber material in FM140 during storage (in Tyvek RfS-bag) at 60%RH/25°C, compared with a bromobutyl having a low moisture content.

Figure 5 : Moisture uptake during storage at 60%RH / 25°C – FM140



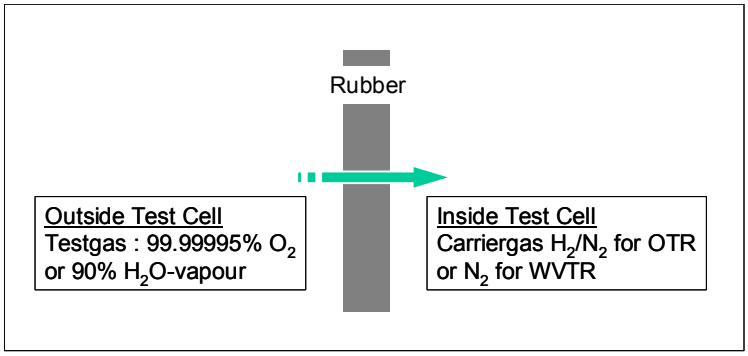
10. Permeability

To be able to obtain permeability data on rubber compounds, a special mould, yielding a thin rubber slab, is used to prepare test pieces.
These rubber slabs, with in this case a thickness of 1.27mm, are preconditioned at 23 °C and 50% Relative Humidity prior to the actual measurement.

For the test itself, a rubber slab is cut matching 50cm², thickness 1.27mm, and clamped in a double chamber test cell, acting as a barrier between both chambers (Figure 6).

The transmission rate is recorded once the system is at steady-state.

Figure 6 : Schematic principle of transmission rate measurement



10.1. Water Vapour Transmission Rate (WVTR)

Tested slabs: **FM140/6 slabs with thickness 1.27 mm**
Equipment: **MOCON, Permatran-W 3/31 MG-module**
Conditions: **38 ° C ; 100% relative humidity ; 100 flow N_2**

Table 5 : WVTR – FM140

	WVTR in g/m².24h, 100% RH / 38°C
FM140	0.06

10.2. Oxygen Transmission Rate (OTR)

Tested slabs: **FM140/6 slabs with thickness 1.27 mm**
Equipment: **MOCON, Oxtran 2/20 ML-module**
Conditions: **38 ° C ; 90 % relative humidity ; 10/20 flow N_2/O_2**

Table 6 : OTR – FM140

	OTR in g/m².24h, 100% RH / 38°C
FM140	71

11. Stability upon gamma irradiation

Due to the penetration gradient of a gamma irradiation treatment, the total irradiation dose of a product is dependent of the location of it in a box, a tote, a pallet, etc. Test pieces in compound FM140 have been gamma irradiated with 2 doses:

- 25 kGy as the generally accepted minimum dose;
- 40 kGy simulating a typical dose for products exposed to the highest irradiation impact.

Non-irradiated test pieces and irradiated test pieces have been evaluated on physical, functional and chemical properties. Physical properties have been evaluated by measuring hardness and compression set. Functional properties were evaluated by measuring fragmentation and needle penetration force and chemical properties by performing a strengthened European Pharmacopeia 3.2.9.

11.1. Effect of gamma irradiation on physical properties

Table 7 : Physical properties after gamma irradiation – FM140

TEST	UNIT	GAMMA IRRADIATION DOSE		
		0 kGy	25 kGy	40 kGy
Hardness	°Shore A	47.8	49.8	50.8
Compression set	%	23.8	27.8	27.7

Both the hardness and compression set of FM140 do not change significantly upon gamma irradiation and this up to doses of 40 kGy.

11.2. Effect of gamma irradiation on chemical properties

11.2.1. Strengthened Pharm.Eur. 3.2.9.

Non-irradiated and irradiated closures in FM140 were subjected to the chemical tests as described in Pharm. Eur. 3.2.9., but exaggerated conditions were used in the pre-treatment, namely the preparation of the aqueous extract:

- uncut rubber closures with a total surface of 200cm² are boiled for 5 min in distilled water and rinsed 5 times with cold distilled water;
- next, a rubber/water ratio of 200cm² rubber/200 ml distilled water was used instead of the Pharm.Eur. ratio of 100 cm² in 200 ml, autoclaved 30min at 121°C.

Table 8 : Chemical properties after gamma irradiation (strengthened Pharm.Eur.3.2.9.) – FM140

CRITERIUM	TEST OBJECT	UNITS	LIMITS	0 kGy	25 kGy	40 kGy
Appearance (430-650 nm)	Sol. S	NTU	Type I : 6.0* Type II : 18*	0.2	0.3	0.3
Colour	Sol. S		See test procedure	pass	pass	pass
Alkaline matter	20 ml S	ml 0.01M HCL ml 0.01M NaOH	0.8 0.3	0.07	0.02	0.08
Absorption 220-360 nm	Sol. S	absorbance	Type I : 0.2 Type II : 4.0	0.02	0.02	0.02
Reducing substances	20 ml S	ml 0.002M $KMnO_4$	Type I : 3.0 Type II : 7.0	0.33	0.13	0.30
Heavy metals	Sol. S	ppm Pb^{2+}	2	< 2	< 2	< 2
Zinc	Sol. S	ppm Zn^{2+}	5.0	0.4	0.3	0.6
Ammonium	Sol. S	ppm NH_4^+	2			
Evaporation residue	50 ml S	mg	Type I : 2.0 Type II : 4.0	0.1	0.4	0.3
Sulphide	20 cm²	mg S^{2-}	0.02	< 0.02	< 0.02	< 0.02

** By definition corresponds with reference suspensions II and II resp.*

Gamma irradiation up to levels of 40 kGy has no noticeable effect on the chemical properties of closures in FM140. All results are within the limits of Pharm. Eur. 3.2.9.

11.3. Effect of gamma irradiation on functional properties

Table 9 : Functional properties after gamma irradiation – FM140

PROPERTY	UNIT	LIMIT	GAMMA IRRADIATION DOSE		
			0 kGy	25 kGy	40 kGy
Penetrability*	N	10	2.20	2.20	2.10
Fragmentation*	average # fragments / 48 piercings	5	0.2	1.9	3.0
Self-sealing°	# vials with discoloration / 10 vials	0	0	0	0

Properties like penetrability, fragmentation and self-sealing are dependent on the closure design. For this test, Datwyler design V9034(*) and V9048(°) were chosen being ISO8362-2 based 20mm injection stoppers. The piercing thickness (relevant dimension for these tests) is 2.20±0.25mm for both stoppers.

Gamma irradiation up to levels of 40 kGy has no noticeable effect on the penetrability and fragmentation performance of closures in FM140. All results are within the limits of Pharm. Eur. 3.2.9.

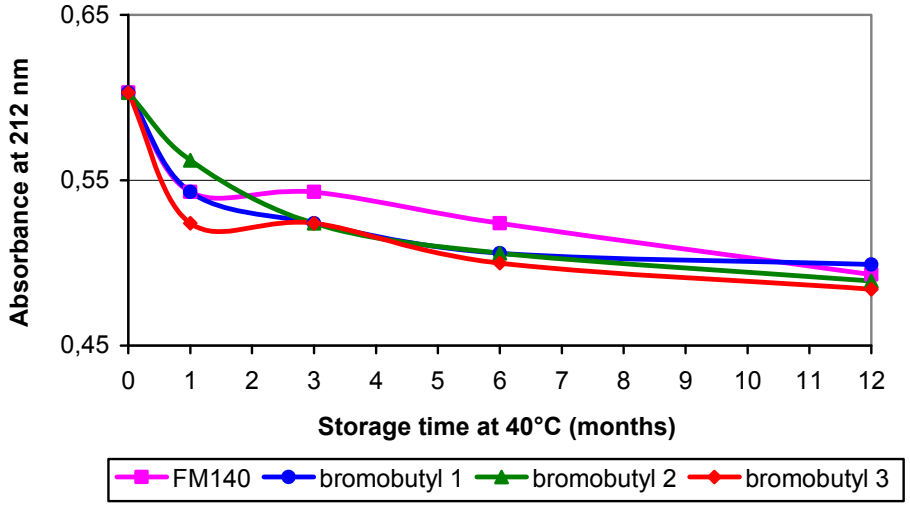
12. Compatibility with preservatives

The goal of this chapter is to investigate the behaviour of FM140 in contact with aqueous solutions containing preservatives that are typically used in parenteral applications.
The behaviour of FM140 is compared with that of other halobutyl compounds.

12.1. m-Cresol

A 0.25 % w/v aqueous solution of m-cresol is stored in contact with rubber at 40°C for up to 12 months.
The surface to volume ratio applied in this test is 30 cm² of rubber surface per 25 ml of a 0.25 % m-cresol solution. The glassware used is type I.
Measuring the UV absorbance of the solution at 212 nm follows up the concentration of the m-cresol.

Figure 7 : Compatibility of FM140 with m-Cresol



12.2. Methyl- and propyl paraben

Aqueous solutions of methyl paraben and propyl paraben of 0.582 g/l and 0.125 g/l respectively are prepared.
20 mm Type I vials are filled with 5 ml of the respective paraben solution and are stoppered with closures in the formulations under test.
After capping, the vials are stored up to 2 months in an inverted position at 40°C in a climate chamber.
The mother solution, where there is no contact with rubber, is equally stored at 40°C.
Measuring the UV absorbance of the solutions at 255 nm follows up the paraben concentration.

Figure 8 : Compatibility of FM140 with methyl paraben

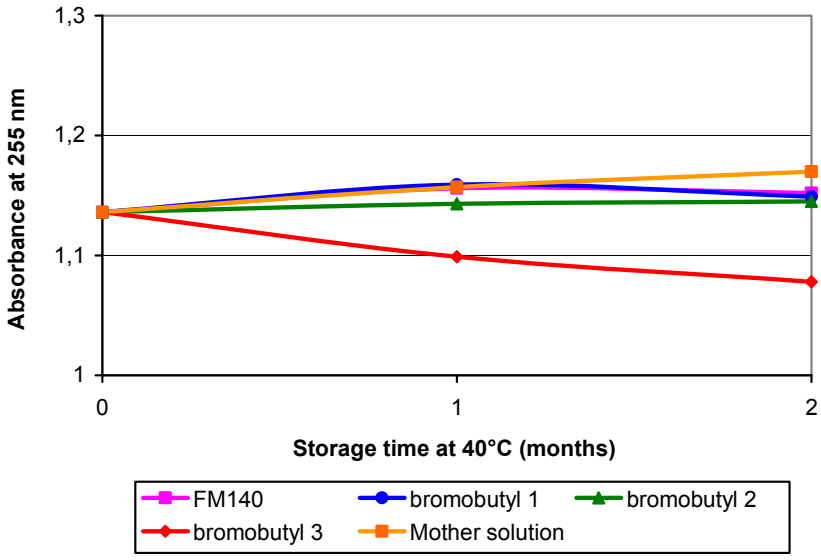
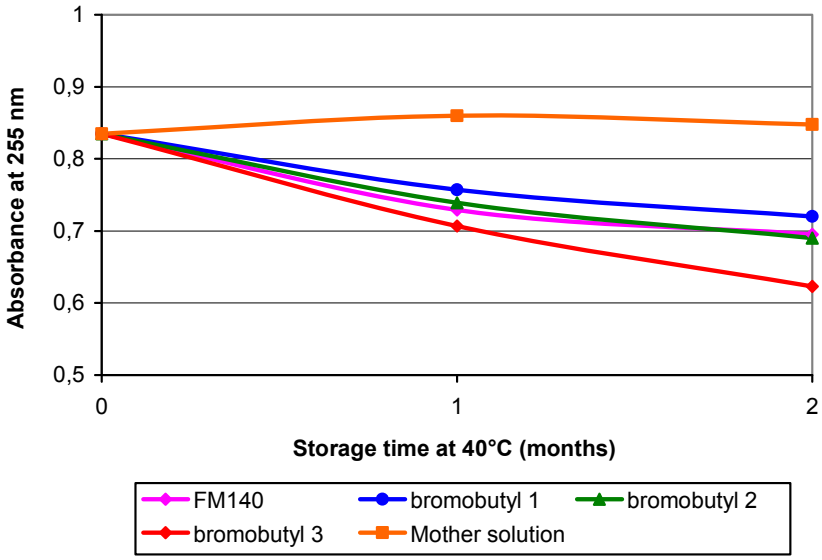


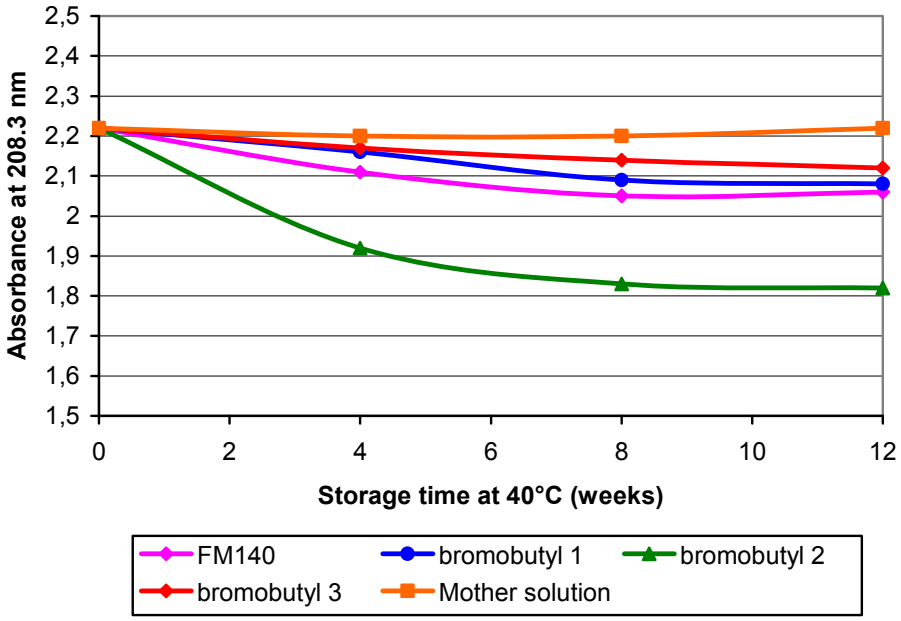
Figure 9 : Compatibility of FM140 with propyl paraben



12.3. Benzalkonium chloride

A 110 mg/l aqueous solution of benzalkonium chloride (BKC) is stored in contact with rubber at 40°C for up to 3 months. The surface to volume ratio applied in this test is 300 cm² of rubber per 80 ml of BKC solution. The glassware used is Type I.
Measuring the UV peaks at 208.3 nm follows up the concentration of the benzalkonium chloride.

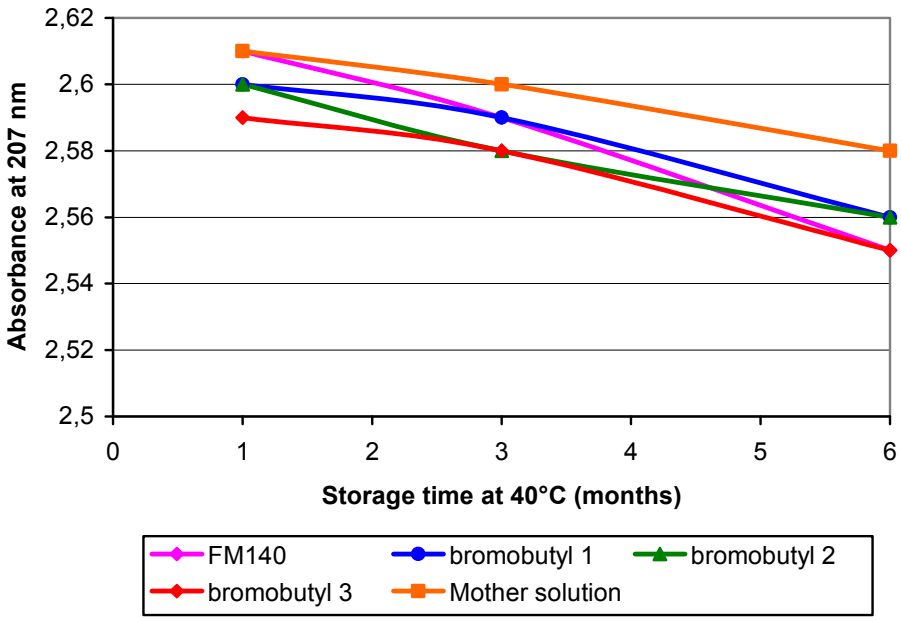
Figure 10 : Compatibility of FM140 with benzalkonium chloride (208.3nm)



12.4. Benzyl alcohol

A 1 % v/v aqueous solution of benzyl alcohol is stored in contact with rubber at 40°C for up to 6 months.
The surface to volume ratio applied in this test is 300 cm² of rubber surface area per 80 ml of benzyl alcohol solution. All glassware used is Type I.
Measuring the UV peaks at 207 nm follows up the concentration of the benzyl alcohol.

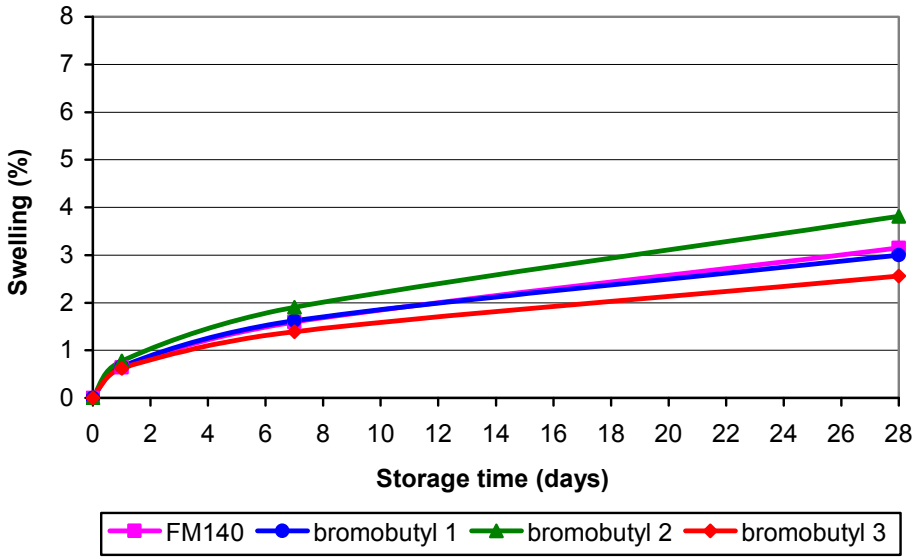
Figure 11 : Compatibility of FM140 with benzyl alcohol (207nm)



13. Compatibility with vegetable oil

Vegetable oil may be used in some parenteral applications.
Halobutyl rubber and vegetable oil are considered to be compatible on the condition that the weight increase of the rubber, as a consequence of contact with the oil, is low. This weight increase, when expressed as a percentage of the original weight of the rubber, is also called “swelling in vegetable oil”.
Peanut oil is used in this test. Storage is at room temperature and goes up to 4 weeks.

Figure 12 : Compatibility with vegetable oil



14. History

Edition (Issue Date)	*Change (chapter + change)*	*Comment (Rationale)*
2 (October 8, 2009)	Chapter 2: Record number update #1994-027	New numbering system at Health Protection Branch Canada
	Chapter 6.1.1.: Update of EP and USP pharmacopeial data	Harmonization between USP<381> and EP3.2.9
	Chapter 6.1.2.: Rephrasing in paragraph 3	/
	Chapter 11.2.2.: “USP after gamma” removed completely	Data has become redundant after harmonization of USP<381> with EP3.2.9