Customer Service Report CS0095

Technical documentation FM257

Edition 3

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1 Table of Contents

2 Description

FM257 is Datwyler's standard bromobutyl 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. FM257 can be seen as a universal rubber compound used in a wide pharmaceutical application range: infusion, injection and lyophilization.

FM257 can be used as rubber compound for both closures for vials as for components for prefilled syringes or cartridges.

FM257 products are not made with natural rubber latex, dry natural rubber latex or any of its derivatives. They are not made using ingredients of animal origin and do not generate known suspicious chemicals like nitrosamines and 2-mercaptobenzothiazole (MCBT). FM257 products are unrelated to BSE/TSE risks. Obviously, these products comply with all major pharmacopoeia for pharmaceutical rubber.

Upon request, products in FM257 can be washed using a validated washing program (ISAF), using Purified Water and Water-for-Injection, and can in combination with sterilizable bags be offered as Ready-for-Sterilisation (RfS).
Tip caps and plunger stoppers in FM257 can be offered in Ready-To-Use (RTU) as well.

Rubber compound FM257 is filed with the FDA in a US Drug Master File (#10953) and with the Health Protection Branch in Canada (#1994-027).

Note: FM257 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

In line with current market expectations, FM257 products are not made with natural rubber latex, dry natural rubber latex or any of its derivatives.

3.2 Nitrosamines

Nitrosamines may be formed starting from residues of specific curing systems. These residues are in a number of cases known to be carcinogenic. FM257 products are formulated without making use of ingredients that potentially give rise to the formation of nitrosamines.

3.3 MCBT

2-mercaptobenzothiazole (2-MBT, 2-MCBT, MCBT) is a rubber chemical that is associated with a health risk. FM257 products do not contain 2-mercaptobenzothiazole (MCBT) or any of its derivatives in their composition.

3.4 BSE/TSE

Rubber compounds may contain components that are of animal origin. Most frequently it concerns fatty acids, fatty acid salts or esters that are either present as active components or as additives to active components. Compound FM257 does not use components of animal origin. FM257 products are in full compliance with the European Pharmacopoeia 5.2.8., “Minimizing the risk of transmitting Animal Spongiform Encephalopathy agents via medicinal products”.

(TSE = Transmissible Spongiform Encephalopathy; BSE = Bovine Spongiform Encephalopathy)

3.5 Heavy Metals

Both US and European legislation impose measures in order to prevent or reduce the impact of packaging and packaging waste on the environment.

FM257 products fulfill the European Community Guideline 94/62/EC for heavy metals in packaging materials. This directive states that packaging components shall not contain more than 100 ppm of Lead (Pb), Cadmium (Cd), Mercury (Hg) and Chromium (VI) (Cr).

EC Guideline 94/62/EC imposes the same requirements as the US CONEG regulation (“Toxics in Packaging Clearinghouse (TPCH)” as established by the coalition of North-eastern Governors (CONEG) in 1992). FM257 products thus also fulfill the CONEG requirements.

3.6 GMO (Genetically Modified Organisms)

FM257 products are not made with ingredients that are derived from Genetically Modified Organisms (GMO).

3.7 Bisphenol A (BPA)

Bisphenol A (BPA) and BPA related substances may be present in certain plastic materials. They are associated with health hazards.

Datwyler confirms that FM257 products do not use Bisphenol A or the following BPA related substances in their composition:

- Polycarbonate
- Polyether sulfone
- Polycarbonate/siloxane co-polymer

- Biostable polyurethanes
- Epoxy resin
- Bisphenol A diglycidylether methacrylate (BIS-GMA)
- Bisphenol A diglycidylether (BADGE)
- Bisphenol A dimethacrylate (BIS-DMA)
- Ethoxylated bisphenol A diacrylates.

4 Shelf life

The shelf life of rubber compound FM257, 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.

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

5.1 Identification properties

The following tests are used to identify the rubber formulation following typical rubber technology standards.

The physical properties as shown in Table 1 are taken for compound FM257/2, 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.

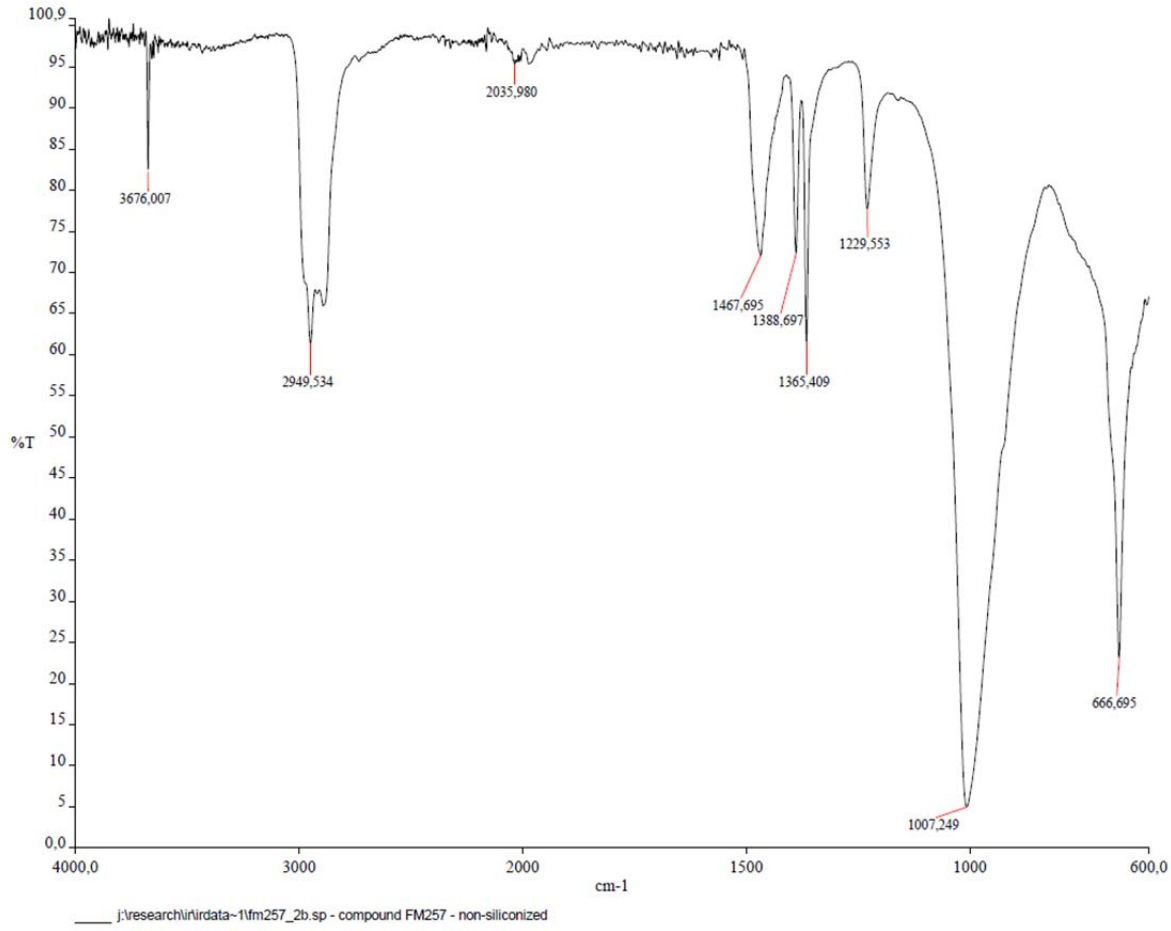
Table 1 : Physical properties – FM257

Hardness	°Shore A	ISO 7619	52 ± 5
Density	g/cm³	ISO 2781	1.355 ± 0.025
Ash	%	Internal Method(s): Calc. 4h@700°C	46.0 ± 2.0
Compression Set	%	ISO 815	max. 17
Tensile Strength	N/mm²	ISO 37	min. 3

5.2 ATIR-FTIR Typical spectrum

Identification of the rubber formulation supplied is quite often part of incoming inspection at Datwyler's customer end. A simple, fast and reliable/robust method is the use of ATIR-FTIR (Attenuated Total Reflectance – Fourier Transformed InfraRed).

Figure 1 : Typical ATR-FTIR spectrum of a cut surface of a product made in FM257



5.3 Permeability

Oxygen and water vapour transmission rates are measured as per ASTM D-3985 (oxygen) and ASTM F-1249 (water vapour). They measure the permeability of a material to oxygen or water vapour.

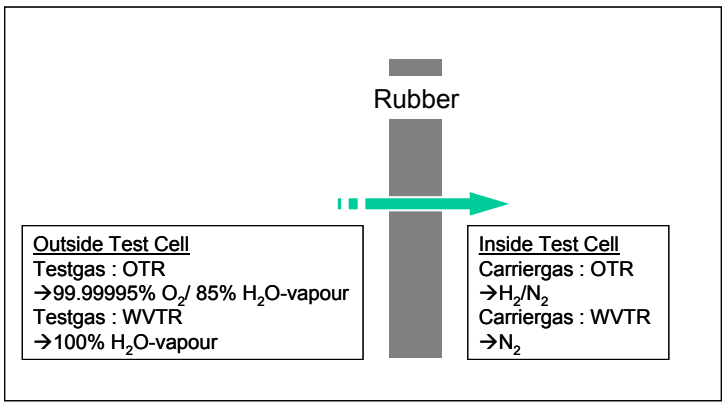
To be able to obtain permeability data on rubber compounds, a special mould, yielding a thin rubber slab, is used to prepare test pieces.

These rubber slabs, with a certain thickness (± 1.3mm), are preconditioned at 23 °C and 50% RH prior to the actual measurement.

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

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

Figure 1 : Schematic principle of transmission rate measurement



5.3.1 Water Vapour Transmission Rate (WVTR)

Tested slabs: FM257/2 slabs with thickness 1.33 mm
Equipment: MOCON, Permatran-W 3/31 MG-module
Conditions: 38 ° C ; 100% relative humidity ; 100% flow N_2

Table 2 : WVTR – FM257

	WVTR in g/m².24h, 100% RH / 38°C
FM257	0.03

5.3.2 Oxygen Transmission Rate (OTR)

Tested slabs: FM257/2 slabs with thickness 1.39 mm
Equipment: MOCON, Oxtran 2/20 ML-module
Conditions: 38 ° C ; 85 % relative humidity ; 99.99995% flow O_2

Table 3 : OTR – FM257

	OTR in cc/m².24h, 85% RH / 38°C, 99.99995% O_2
FM257	48

6 Chemical Properties

6.1 Pharmacopoeial 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 FM257 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 and Figure .

Table 2 : Pharm.Eur.3.2.9./USP<381> data, chemical part – FM257

Characteristic		Amount tested	Units	Limit	Typical Value	
Appearance of solution	Turbidity	Sol. S	NTU	Type I: 6.0 *(*)* Type II: 18.0 *(*)*		0.3
	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		0.01
Reducing substances		Sol. S (20 ml)	ml 0.002M $KMnO_4$	Type I: 3.0 Type II: 7.0		0.3
Extractable heavy metals		Sol. S	ppm Pb^{2+}	2	EP	<2
					USP	<2
Extractable zinc		Sol. S	ppm Zn^{2+}	5.0		<0.01
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		0.1
Volatile sulphides		20 cm²	mg S^{2-}	0.02		<0.02

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

For FM257 products Datwyler guarantees a shelf life period of 2 years after the packing date.

Compliance of FM257 with the chemical requirements of Pharm.Eur. 3.2.9 and USP <381> after 2 years shelf life is demonstrated in the table below.

Table 3 : Pharm.Eur.3.2.9./USP<381> data, chemical part – FM257

Characteristic		Amount tested	Units	Limit	Typical Value	
Appearance of solution	Turbidity	Sol. S	NTU	Type I: 6.0 *(*)* Type II: 18.0 *(*)*		0.2
	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 EP USP	0.06 0.06 0.00
Absorbance		Sol. S	A_{max}220-360 nm	Type I: 0.2 Type II: 4.0		0.01
Reducing substances		Sol. S (20 ml)	ml 0.002M $KMnO_4$	Type I: 3.0 Type II: 7.0		0.2
Extractable heavy metals		Sol. S	ppm Pb^{2+}	2	EP USP	<2 <2
Extractable zinc		Sol. S	ppm Zn^{2+}	5.0		<0.01
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		0.03
Volatile sulphides		20 cm²	mg S^{2-}	0.02		<0.02

** By definition corresponding with reference suspensions II and III resp.*
(Data recorded for batch 30036689 after 2 years shelf life)

Figure 2 : Typical IR-spectrum (4000-625cm^{-1}) of a pyrolysate (according to Pharm. Eur. 3.2.9.) – FM257

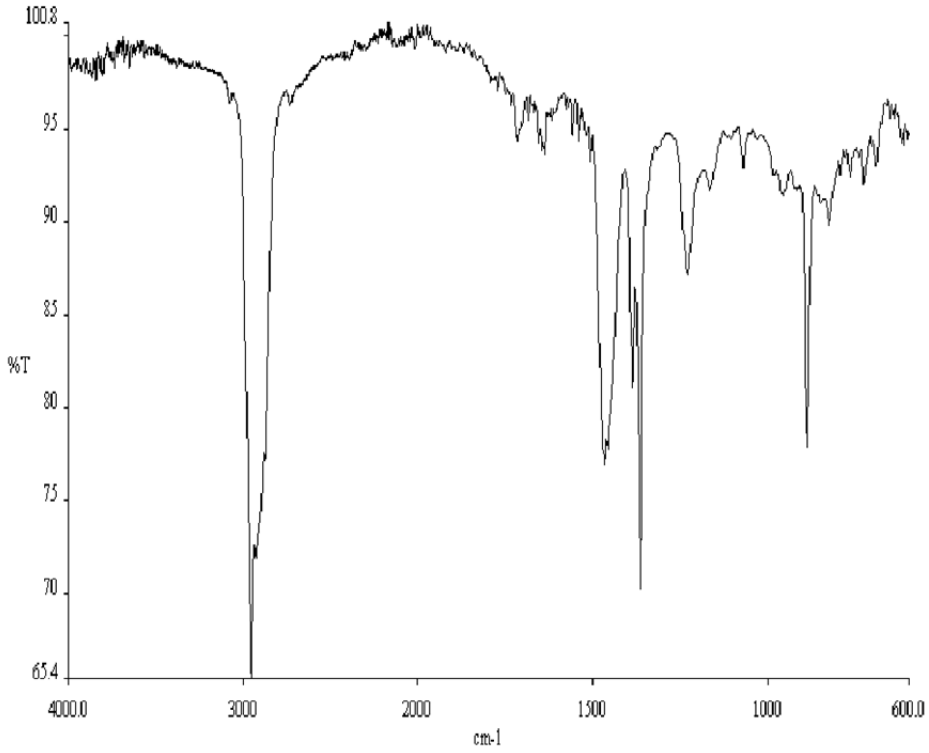
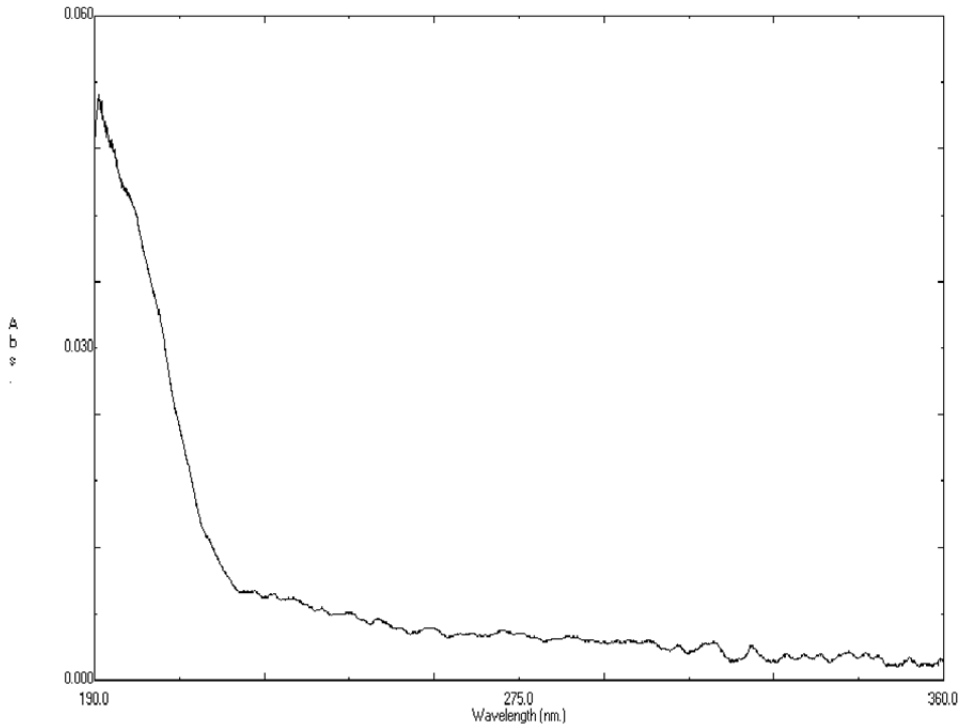


Figure 3 : Typical UV-spectrum of an aqueous extract (according to Pharm. Eur. 3.2.9.) – FM257



6.1.2 Japanese Pharmacopeia 7.03

Results for FM257/0, 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 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 a standard Datwyler 13mm lyophilisation closure (V9212) with a volume of 0.55 cm^3, a weight of 0.75 g and a total surface of 6.45 cm^2 in compound FM257/0. Larger stopper designs expectedly will show results that are as least as good, since the surface/volume ratio of such stoppers is smaller (less rubber surface in contact with the extraction medium).

For the design given, FM257 complies with the extractable substances part of the Pharm. Jap. 7.03.

Table 4 : JP 7.03 „Extractable substances" – FM257

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	100.0 99.9
Foam test	5 ml	-	foam disap. < 3 min.	Pass
pH	20 ml	pH units	Difference with blank: max. 1.0 (*)	-0.09
Reducing substances	100 ml	ml 0.002 M $KMnO_4$	2.0	0.67
Evaporation residue	100 ml	mg	2.0	0.38
UV absorb. (220-350 nm)	10 mm cuvet	absorbance	0.2	0.01
Zinc	10 ml	ppm Zn^{2+}	1 ppm	<0.01

(*) "-" means more acidic than blank; "+" means more alkaline than blank
(Data recorded for batch 30212301)

The results of other parts of Pharm. Jap. 7.03 carried out on the same batch were as follows :

Table 5 : JP 7.03 „Cadmium, Lead, Acute Systemic Toxicity, Pyrogen Test, Hemolysis test" – FM257

TEST	LIMIT	RESULT
Cadmium	5 ppm	<0.001 ppm
Lead	5 ppm	1.19 ppm
Acute Systemic Toxicity	Limit test	Pass
Pyrogen Test	Limit test	Pass
Hemolysis Test	Limit test	Pass

(Data recorded for batch 30212301)

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 in an earlier part of this section.

6.3 Extractable information

A detailed extractables report on FM257 involving solvents of various polarities, is available on request.

Because of their confidential nature, the results of this extractables study are not given in full detail in this report. They will be available only after conclusion of specific agreements. Please contact your Datwyler sales representative.

7 Functional Properties

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

Table lists the functional properties of FM257 as per the Pharm. Eur. 3.2.9 / USP <381>.

7.1.1 Penetrability

Principle

The force needed to completely pierce an elastomeric closure is measured using a universal force tester.

Sample preparation

10 closures are pretreated as described in Pharm.Eur. 3.2.9 / USP <381>:

• The closures are placed in a glass container, covered with distilled water and boiled for 5 minutes. They are rinsed 5 times with cold distilled water.

• The washed and rinsed closures are placed in a conical flask and covered with distilled water (2 ml per cm² of rubber surface area).

• The closures are autoclaved at 121°C for 30 minutes.

• The water is decanted and the closures are allowed to dry at room temperature.

Procedure

• 10 clean, standard 20 mm vials are filled with water to their nominal volume.

• The filled vials are closed with the rubber closures under test and capped with an aluminium seal.

• The closures are pierced with a 0.8 mm (21 G) hypodermic needle at a controlled speed of 200 mm/min and the force required to pierce the closure is recorded.

• The piercing force should not exceed 10 N.

7.1.2 Fragmentation (coring)

Principle

Elastomeric closures for injection vials are pierced with an injection needle. Elastomeric fragments which have been caused by piercing are collected on a filter and counted.

Sample preparation

12 closures are pretreated as described in Pharm.Eur. 3.2.9 / USP <381> (see above for description).

Procedure

• 12 clean, standard 20 mm vials are filled with 5 ml of water.

• The vials are closed with the closures to be examined and secured with an aluminium seal.

• A clean syringe is filled with distilled water .

• A hypodermic needle with external diameter 0.8 mm (21 G) is fitted to the syringe.

• The first closure is pierced, 1 ml of water is injected and 1ml of air is removed.

• This operation is done 4 times for each closure with one and the same needle. The closure is pierced at a different site each time

• A new needle is taken for each subsequent new closure.

• The liquid from 12 vials is filtered over a filter with a pore size of 0.5 µm.

• The fragments on the filter are counted by naked eye.

• The total number of fragments per filter (resulting from 12 x 4 = 48 piercings) may not exceed five.

7.1.3 Self-sealing

Principle

Determine the resealability of a rubber closure, after being punctured with a needle. The test medium is an aqueous solution.

Sample preparation

10 closures are pretreated as described in Pharm.Eur. 3.2.9 / USP <381> (see above for description).

Procedure

• 10 clean, standard 20 mm vials are filled with water, closed with the closures to be examined and secured with an aluminium seal.

• Each stopper is pierced 10 times with a hypodermic needle with external diameter 0.8 mm (21 G).

• The vials are immersed upright in a 0.1% methylene blue solution

• The external pressure is reduced with 27 kPa for 10 min.

• The atmospheric pressure is reestablished and the vials are left immersed for 30 min.

• The vials containing any trace of coloured solution are counted

• The limit is zero vials with coloured solution.

The results shown in Table below are for a typical 20mm serum stopper.

Table 6 : Pharm.Eur.3.2.9./USP<381> Functional tests – FM257

TEST	UNITS	LIMIT	TYPICAL RESULTS	STATISTICAL RESULTS (*)
Penetrability	N	10	2-3	AVG=2.6; σ = 0.21; # = 405
Fragmentation	-	5	0	AVG=0,5; σ = 1.0; # = 405
Self-Sealing	-	0	0	AVG=0; σ = 0; # = 405

(*) Statistical results are obtained from the Datwyler SAP computer system for the combination V9048 in FM257 (period 01/01/2009 – 31/12/2010)

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 .

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 FM257 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 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.

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TEST RESULT REPORT

BELAC

Project Number:	**TE 09968**	**Study Number:**	**09-B2506-N1**
Sponsor:	**Helvoet Pharma Belgium NV**	**Report Date:**	**24/12/2009**
Contact:	*Mrs. Nadia Nouri*		
Address:	Industrieterrein Kolmen 1519 3570 Alken, Belgium	Date Sample Arrival: Technical Initiation:	18/12/2009 21/12/2009
PO Number:	PB0904230	Technical Completion:	24/12/2009

Study	**Elution Test - ISO**	Temp/Time	37°C/24 hours
Test Item	FM257/2 V9250 SAF1	Ratio	25cm²/20mL
Lot	30171994	Vehicle	MEM-Complete

REFERENCE: According to "ISO 10993-5, 2009: Biological Evaluation of Medical Devices- Part 5:Tests for In Vitro Cytotoxicity." and "USP 32-NF 27, 2009: <87> Biological reactivity test, in vitro." Toxikon Reference: SOP 3.1.2.3, rev. 08

PROCEDURE: The biological reactivity of a mammalian monolayer, L929 mouse fibroblast cell culture, in response to the test item extract was determined. The samples and control articles were autoclaved prior to the preparation of the extracts. Extracts were prepared at 37±1°C for 24 hours in a humidified atmosphere containing 5±1% carbon dioxide (static). Positive (natural rubber) and negative (silicone) control articles were prepared to verify the proper functioning of the test system. The maintenance medium on the cell cultures is replaced by the extracts of the test item or control article in triplicate and the cultures are subsequently incubated for 48 hours, at 37±1°C, in a humidified atmosphere containing 5±1% carbon dioxide. Biological reactivity was rated on the following scale: Grade 0 (No reactivity); Grade 1 (Slight reactivity), Grade 2 (Mild reactivity), Grade 3 (Moderate reactivity) and Grade 4 (Severe reactivity). The test item is considered non-cytotoxic if none of the cultures exposed to the test item shows greater than mild reactivity (Grade 2).

RESULTS: No reactivity (Grade 0) was exhibited by the cell cultures exposed to the test item at the 48 hours observation. Severe reactivity (Grade 4) was observed for the positive control article. The negative control article showed no signs of reactivity (Grade 0).

CONCLUSION: Based on the evaluation criteria mentioned above, the test item is considered non-cytotoxic.

RECORD STORAGE: All raw data generated in this study will be archived at Toxikon Europe, according to SOP 4.2.8.

AUTHORIZED PERSONNEL

for ir. Peter Cornelis
Study Director

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Quality Assurance

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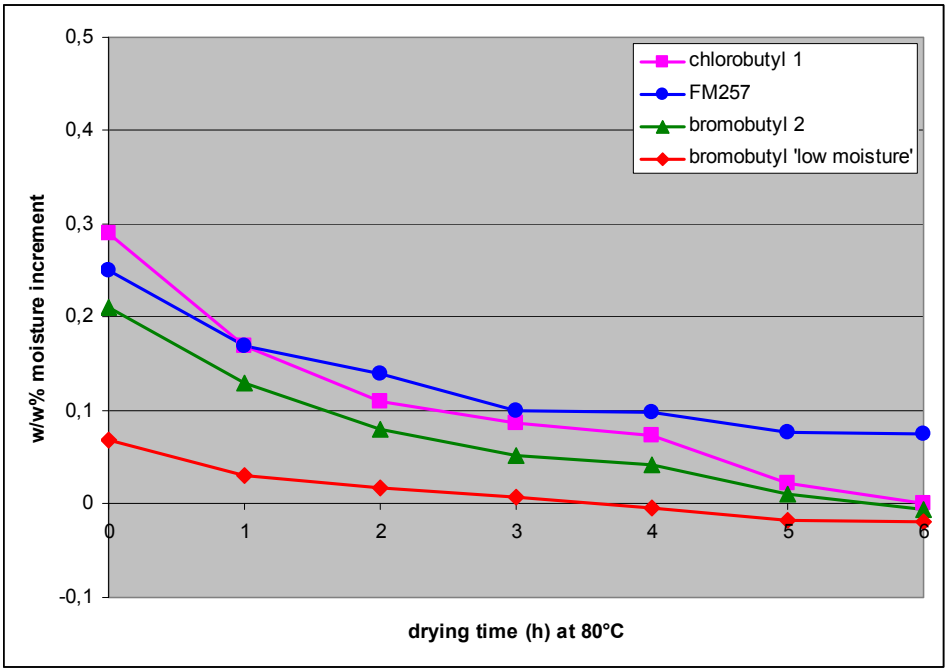
9 Moisture Content

Results for moisture content that are given below are indicative only as the actual moisture content is dependent on numerous factors like stopper design, packaging way, climate, actual steam sterilization and drying equipment, etc.

The typical moisture content of rubber compound FM257 after the final treatment at Datwyler, i.e. after washing, drying and packaging, is in the range of 0.3 w/w% (3 mg water/g rubber).

Additional moisture is absorbed during the steam sterilization step. The graph below shows the uptake of some standard compounds after steam sterilization and the moisture release upon drying at 80°C.

Figure 2 : Moisture uptake after autoclaving 30min at 121°C and moisture release after drying at 80°C



10 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 FM257 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 a strengthened European Pharmacopeia 3.2.9.

10.1 Effect of gamma irradiation on physical properties

Table 7 : Physical properties after gamma irradiation – FM257

TEST	UNIT	GAMMA IRRADIATION DOSE		
		0 kGy	25 kGy	40 kGy
Hardness (ISO7619)	°Shore A	51.3	52.2	52.6
Compression set (ISO815)	%	12.7	15.0	17.7

Changes in hardness upon gamma irradiation are negligible. An increase in compression set can be seen after gamma irradiation.

10.2 Effect of gamma irradiation on chemical properties

Non-irradiated and irradiated closures in FM257 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, and autoclaved 30min at 121°C.

Table 8 : Chemical properties after gamma irradiation (strengthened E.P.3.2.9.) – FM257

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*	0.3	0.6	0.4
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	0.08	0.03	0.08
Absorption 220-360 nm	Sol. S	absorbance	Type I : 0.2 Type II : 4.0	0.01	0.02	0.02
Reducing substances	20 ml S	ml 0.002M $KMnO_4$	Type I : 3.0 Type II : 7.0	0.43	0.20	0.33
Heavy metals	Sol. S	ppm Pb^{2+}	2	< 2	< 2	< 2
Zinc	Sol. S	ppm Zn^{2+}	5.0	0.0	0.1	0.1
Ammonium	Sol. S	ppm NH_4^+	2	< 2	< 2	< 2
Evaporation residue	50 ml S	mg	Type I : 2.0 Type II : 4.0	0.4	0.5	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 FM257. All results are within the limits of Pharm. Eur. 3.2.9., even considering the exaggerated conditions.

10.3 Effect of gamma irradiation on functional properties

Table 9 : Functional properties after gamma irradiation, procedure acc. the Pharm.Eur.3.2.9. – FM257

PROPERTY	UNIT	LIMIT	GAMMA IRRADIATION DOSE		
			0 kGy	25 kGy	40 kGy
Penetrability*	N	10	2.30	2.50	2.90
Fragmentation*	average # fragments / 48 piercings	5	1.8	6.0	7.2

Properties like penetrability and fragmentation are dependent on the closure design. For this test, Datwyler design V9034(*) was chosen being a standard 20mm injection stopper. The piercing thickness (relevant dimension for these tests) is 2.20±0.25mm.

The Pharm. Eur. 3.2.9. stipulates a limit of 5 fragments on 48 piercings. This may become borderline for compound FM257 after a gamma irradiation treatment. On this basis, compound FM257 is not recommended for multi-dose applications in combination with a gamma irradiation sterilization step.

11 Compatibility with preservatives

The goal of this chapter is to investigate the behaviour of FM257 in contact with aqueous solutions containing preservatives that are typically used in parenteral applications.

The behaviour of FM257 is compared with other halobutyl compounds.

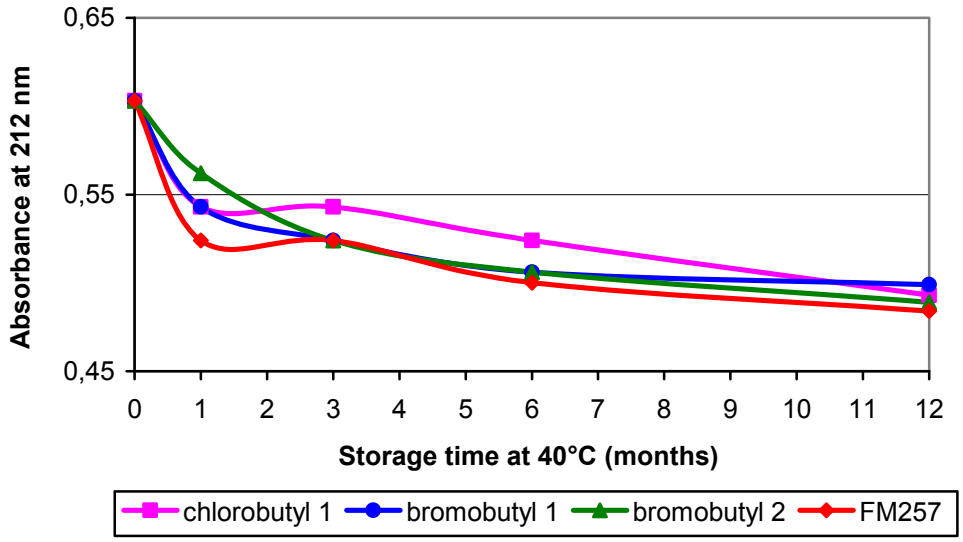
11.1 m-Cresol

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 5 : Compatibility of FM257 with m-Cresol



11.2 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 6 : Compatibility of FM257 with methyl paraben

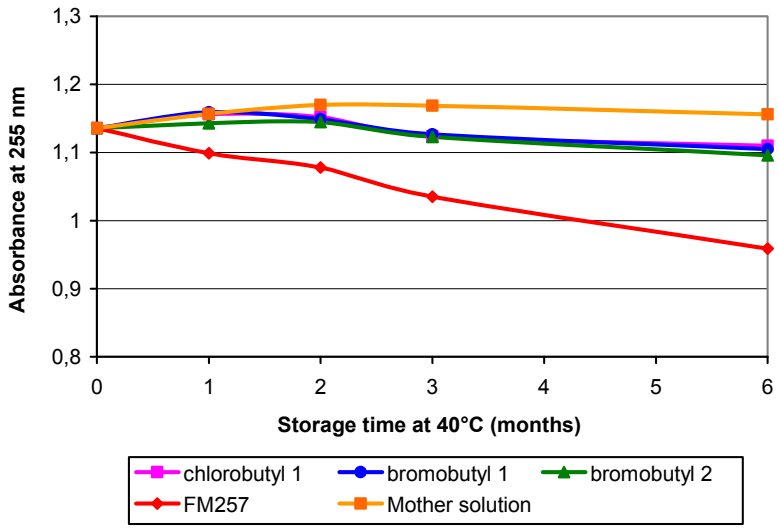
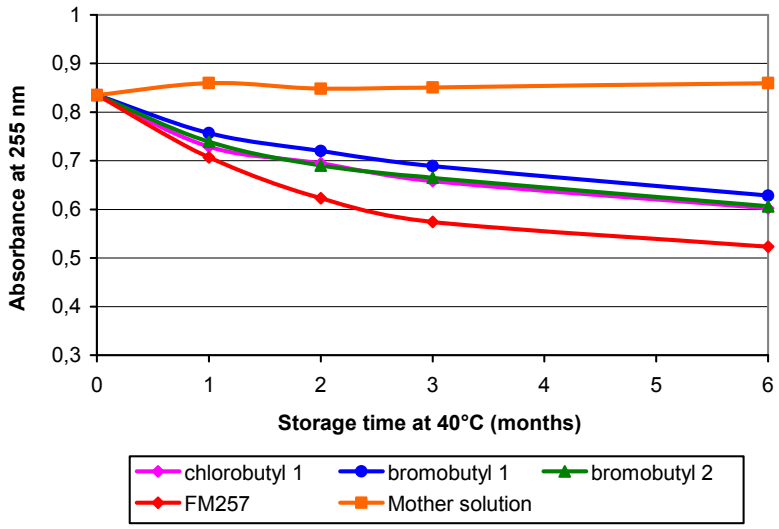


Figure 7 : Compatibility of FM257 with propyl paraben

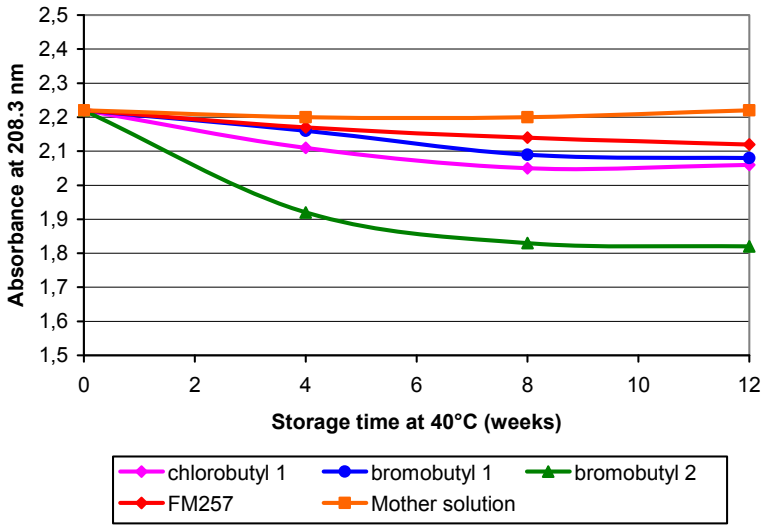


11.3 Benzalkonium chloride

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 8 : Compatibility of FM257 with benzalkonium chloride (208.3nm)



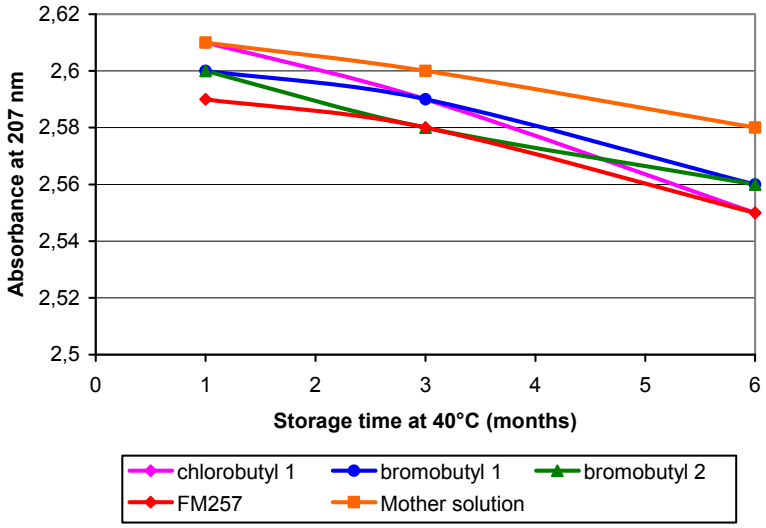
11.4 Benzyl alcohol

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 9 : Compatibility of FM257 with benzyl alcohol (207nm)



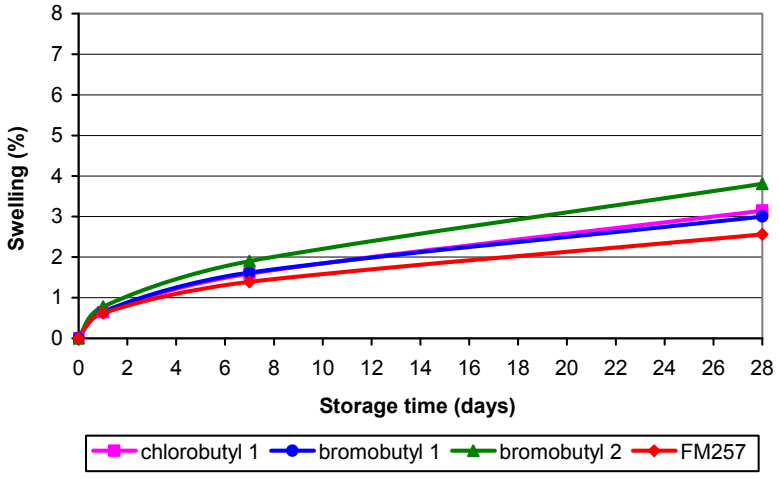
12 Compatibility with vegetable oil

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 10 : Compatibility with vegetable oil



13 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 4: 1-year gamma irradiated shelf life statement removed	FM257 is not recommended when used in combination with gamma irradiation sterilization
	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
3 (November 23, 2012)	Helvoet Pharma replaced by Datwyler throughout the whole document	Name change
	Chapter 2 + 3: ingredient statements adjusted	Updated statements available
	Chapter 10 (permeability) integrated in chapter 5 (physical properties) and rephrased permeability data	Layout change
	Chemical data after 2 years shelf life added in chapter 6.1.1	New data available
	Replaced JP data with more recent ones (chapter 6.1.2)	New data available
	Added chapter 6.3 (extractable information)	
	Rephrased functional properties (chapter 7.1) + replaced data with more ones	More explanation on functional properties + more recent data available
	Chapter 8: replaced Toxikon certificate with more recent	More recent certificate available
	Chapter 9: rephrasing	