

Carboxymethyl cellulose (CMC) hydrogels for the filling of implants. Our experience since 15 years.

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Summary

Summary - hydrogel pre-filled breast implants. Our experience since 15 years.

The author reports 15 years of laboratory and surgical experience in the use of breast implants pre-filled with carboxy-methyl-cellulose gel which he has used since 1984. Laboratory tests and results are presented. The author has undertaken a retrospective analysis of 380 clinical cases since 1984. He concludes that there is a future role for breast implants containing a non-toxic, visco-elastic and biodegradable filling gel in conjunction with the manufacture of increasingly reliable implant linings.

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breast implante / hydrogel

After 35 years of practice, we can summarise our experience with breast implants in *Table I*.

From 1965 to 1970, we used implants that can be filled with saline, which we developed in 1965 for 420 patients.

We abandoned these refillable saline implants gradually from 1970, for the following reasons:

- Leakage due to the fill valve and the manufacturing technique of the time [1]
- Poor adaptation of the container to content (folds)
- Length of the intervention
- Risk of infection due to multiple manipulations during the operation.

From 1970, we have used exclusively implants pre-filled silicone gels, for 840 patients, obtaining the best results.

However, in 1980, we became aware of the growing number of long-term local complications: intracapsular ruptures rarely diagnosed and sometimes with extracapsular fissurations, presence of foreign body tumours [2] in the breast tissue, muscle or subcutaneously near the implant as a consequence of silicone gel leakage.

Table I experience the author				
Types of breas timplants	Numbers of patients by period			
	1965	1970	1984	1995
Filled with physiological serum	420			
Prefilled with silicone gel		840		
Prefilled with CMC gel			380	
Filled with physiological serum				28

CMC: carboxymethyl cellulose

After twenty re-operations whose postoperative were were random, we decided in 1983 to study another filler harmless, biodegradable or readily eliminable. Our choice fell on a carboxymethyl cellulose (CMC) gel dissolved in saline.

We shall examine here the reasons for this choice, the laboratory examinations and our surgical experience with about 380 cases since 1984, with 90% of cases due to aesthetic considerations and 10% based on indications of surgery.

After 1995, the CMC gels were prohibited and subjected in France to further testing for manufacturing authorisation for export. This investigation was requested from an independent laboratory that concluded in favour of the safety of CMC for the proposed use. These tests confirmed what we had established ten years ago.

CARBOXYMETHYL CELLULOSE (CMC)

CMC is a cellulose polysaccharide of carboxy-methyl at a certain degree of substitution of hydroxyl radicals.

The CMC is soluble in all proportions in water or serum, transparent solution having a molecular weight of around 10,000.

The gels obtained are physical gels, without cross-linking, that is to say, the viscosity depends essentially on the concentration.

The viscosity of these gels is also stable over time.

Their osmotic properties follow the Van t'Hoff law of thermodynamics.

Their oncotic pressure is low.

The molecular stability is good in aqueous media, at temperatures from 10 to 130 °C, for a wide range of pH (2 <pH <10).

No effect on the physical properties of silicone elastomers have been detected.

Arguments on presumptive safety of CMC

Cellulose is the carbohydrate or polysaccharide derived from photosynthesis, the most common in nature.

Its preservation and stability except regarding microorganism is legendary, even in salt water environment.

It represents the building blocks of all plant life.

It has never been considered as toxic.

Cellulose dressings in contact with the sores have the best reputation for tolerance. Eighty per cent of dust we breathe all our lives is cellulose!

Arguments on objective safety of CMC

Some cellulose based suture threads (flax threads) never showed intolerance with living tissue.

Methyl cellulose is a vector of eye drops. [3]

Polysaccharides have been used in a large number of drugs by the pharmaceutical industry and as a substitute for blood plasma [4-6].

The few published cases of allergy remain questionable and exceptional.

CMC was used in intraperitoneal injections to prevent mesenteric adhesions.

EXPERIMENTAL STUDY

The experiment was conducted in two phases:

- The first comprehensive experimental base was completed in 1984
- The second experiment resulted in many additional tests for European approval (CE marking) and was conducted from 1995 to 1998.

Global tests of 1984

The objective was to show the overall safety of CMC on animals.

Injections of CMC 4% gel in saline were made on rabbits at doses increasing from 1 to 10% of body weight in subcutaneous abdominal injections, which corresponds to a quantity of 6 kg gel for a 60 kg woman!

The results are summarised in Table II.

On a general level, the weight gain remained comparable to control animals.

Locally, oedema reaction was observed, significantly increasing the volume of injection. It disappeared spontaneously within a few days depending on the injection volume

Table II Results of subcutaneous injection of CMC gel in rabbits			
Quantity of CMC gel 4% injected in grams	Local reactions after 8 days	General reaction after 8 days	Reaction on descendants after one year
20	None	None	None
50	Slight oedema	None	None
100	Oedema	None	None
200	Oedema	Lack of appetite	None

CMC: carboxymethyl cellulose

At histology, during the first month, a major macrophage influx was noted. During the second month, we noted the disappearance of macrophages in favour of a slight scarring. After the sixth month the injection lacunae could not be found. No microscopic difference between the injection zone and adjacent tissues was identified.

Beyond the extrapolations required in laboratory, we must remember that the subcutaneous injection of a dose of CMC gel 4% of 100th weight of the animal, at one time, which corresponds to clinical reality of breast implant rupture, has never demonstrated any toxicity of CMC subcutaneously.

Injections at increasing doses of 10 cm³ to 50 cm³ of the same gel (4% CMC) were made intravenously in the ear vein of the rabbit.

The results are summarised in *Table III*.

Specific tests of 1996

The biodegradability of hydrogels depends on their method of preparation, the degree of substitution and polymerisation. As opposed to some chemical hydrogels little or non-degradable, CMC is biodegradable into compounds of low energy gradient (glucose in beta and CO₂ and H₂O).

We reproduce here the extracts of findings in the official report made to the Ministry of Health in France by the LEMI laboratories (Technopole Martillac, France).

The most significant tests are summarized in *Table IV*.

It must be added that the study of mutagenesis and chromosomal alterations was negative.

The conclusion of the laboratory LEMI is as follows: "The CMC is a semi-synthetic compound that appears to be devoid of toxicity."

It is particularly interesting for the filling of breast implants.

The final product of degradation is glucose.

Table II Results of subcutaneous injection of CMC gel in rabbits		
Quantity of CMC gel 4%	Immediate clinical signs	Clinical signs after one month

injected intravenously (ml)		
1	None	None
10	None	None
50 (injections in less than 10 seconds)	Death by cerebral embolism (immediate mydriasis)	

CMC: carboxymethyl cellulose

Table IV: Results of cellular tolerance analyses (Laboratoire LEMI).

	Results
Cytotoxicity	Nil
Acute toxicity	Nil
Dermal irritation	Nil
Sensitisation	Nil
Haemocompatibility	Good
Mutagenesis	Nil

CMC: carboxymethyl cellulose

Stability over time, osmosis and influence on the envelope of implant

Although cellulose has a reputation for good chemical stability in salt water environment in time, we wanted to verify this in 1983 and studied the osmotic properties of the wall of the implant in the presence of CMC hydrogel.

Stability over time

Several experiments have been conducted. Under normal conditions (20 °C, atmospheric pressure, sterile environment) viscosity (measured by flow time) and the physical appearance of the hydrogel have not changed in three years.

Artificial ageing experiments (15 days at 2 bar and 120 °C) showed no significant difference (relative error allowed on manipulations and measures: 3 %).

It should be noted, however, that beta or gamma radiation (5-10 kGy) are very active on the physical properties of CMC gels. They determine the liquefaction of gels. This fact alone precludes sterilisation by radiation.

Osmotic properties

Although the transfer time is relatively long with silicone elastomer membranes, it is surprising to find an osmotic passage with a large dielectric strength of the order of several megohms per cm². There is therefore no ionic transfer of water or salt. The passage of water in molecular form takes place clearly based on differences in concentrations of dissolved salt. If this passage is obvious for a saline-filled implant immersed in a bath of deionized water (1-2 mg/h/dm²), it is no longer significant in a bath of serum or serum for implants or for serum hydrogel implants.

This precise experiment has convinced us not to reduce the amount of sodium chloride in the serum in order to compensate for possible low oncotic pressure of the CMC.

It should be noted that no osmosis is involved when there is a leakage of the implant. Free in the surgical cavity, CMC determines an aqueous influx the occurrence of which obeys a different phenomenon because there is no longer a membrane. This phenomenon indicates the highly hydrophilic nature of CMC. This is why the increase in volume, clinically detectable, is pathognomonic of the leak.

Influence on the envelope

Even with considerable concentrations of CMC in the implant, it was impossible to find traces of CMC in the water of soaking baths. Mechanical tests (elongation, tensile strength, Young's modulus) remained the same. This leads to the conclusion that the CMC has no chemical or physical affinity with the wall of the implant.

Tests of creep-hardening in a fold that explain in most cases, the percentage of leakage with serum implants are almost impossible to obtain on a silicone elastomer membrane in contact with a CMC gel. This may be due to the extremely slippery nature of the CMC gel on the wall of the implant that allows continual shifting of fatigue sites.

CLINICAL EXPERIENCE

Breast implants pre-filled with CMC gel were sold in France from 1985.

For us, indications for surgery were the same as for other pre-filled implants.

In general:

- Retromuscular position was reserved for aplasia
- Pre-muscular position was chosen when the glandular and subcutaneous tissues were thick enough
- The approach pathn chosen by the patient and the surgeon, was inframammary, axillary or transareolar.

Incidents and complications

Infections

No infection was found among 380 patients operated.

Leaks or ruptures

We had observed in 1986 and 1987 ten ruptures CMC hydrogel implants due to a manufacturing defect of the envelope (detached patch).

If these incidents were naturally bad experiences with an obligatory change of implants, we have, however, gained a lot in terms of clinical experience.

Indeed, the separation of a patch causes a rapid effusion of the contents of the implant.

We have thus observed in our patients phenomena we had already observed in animals. Within eight days following the "puncture" appears oedema in reaction without other clinical signs (no pain, no redness, no temperature). The anxious patient returns to consult with us whether we have not made a mistake on the size of an implant. The oedema reaction has convinced us of the leak and allowed operating again quickly. Early diagnosis of "puncture" is a big advantage that prevents retraction of the detachment cavity that occurs in leaks with saline implants at a later re-operation [7].

It may be remembered here that, when the contents of a breast implant is not degradable (such as silicone gels) or low degradable (such as fatty acids, soybean oil or other), the diagnosis of "puncture" is late, resulting in either local retractile reactions of mesenchyme, or foreign body tumours.

Early re-operation during a leak of CMC is extremely simple and can be performed under local anaesthesia without having to redo a surgical detachment.

We never had a problem replacing these implants from a technical point of view as well as a psychological point of view, because our patients have always been quite well informed of the possibility of a leak or rupture leading to a change of implant and the mildness of the re-operation.

We have seen, by intraoperative sampling, what we had already seen in animals: the macrophage influx little inflammatory, indicator of the degradation or elimination of the CMC. It was enough, in all cases, to clean the cavity with saline or hydrogen peroxide (5 to 10 vol.) and replace the implant to get everything in order within two or three days.

Two patients, who returned consult five years after surgery for a gradual deflation on one side, we were naturally forced to surgically rebuild the cavity that had shrunk around the empty pocket of the implant. The walls of this cavity showed no abnormality in thickness, no inflammatory granuloma, no foreign body tumour [8].

The ruptures (excluding the manufacturing defect of 1986) are summarised in *Table V*.

These results show no significant difference compared to the usual reports accepted in the literature: approximately 4 to 6% deflation in ten years.

Year	Accidental or sudden intraoperative rupture	Long-term leakage and re-operation	Related clinical signs
1990	1	7	Most often none
	2	17	Sometimes painful discomfort on mobilisation of the implant
1998	0	15	More obvious in the case of retractile shell

However, considerable technical progress, especially in the development of autogenous welding of patch, show much better long-term statistics that it is too early to publish.

It is quite remarkable that, contrary to what happens with silicone gels [2, 9], mechanical properties of the shell are not affected by water solutions of CMC.

Capsular contractures

We observed:

- Three short-term capsular contractions (three to four months after surgery), stage III Baker
- Ten long-term capsular contractions (four to five years after surgery), stages III and IV.
- We changed the implants after enlarging the surgical cavity.

This classic complication with all implants compels us to give here our views on the etiology of capsular contractions [10-12].

After a long experience, both clinical and laboratory, it seems that the fibroblastic reaction and fibrocytary shrinkage have little or no relation to the nature of the implant.

This reaction may have a different etiology depending on the time of occurrence:

For short term capsules

- Inadequate surgical separation in response to slight compression of the implant during the healing
- Post-operative haematoma, even very small (called lenticular haematoma), phagocytosis of degradation products of fibrin that is always of fibrocytary and retractile evolution, sometimes with calcium deposits (which is why absolute quiet must be ordered during four to five days after the operation).

For long term capsules

- The transudation of non-degradable fillers (bleeding) by transfibrocytary phagocytosis, with or without associated inflammatory granulomas
- The normal development of all mesenchymal wrapping of a chemically stable foreign body. The capsular contracture represents the natural tendency to establish a natural surface to volume ratio as small as possible with living tissue.

CONCLUSION:

After more than 35 years of using breast implants, we are now entitled to demand maximum reliability of our implants regarding both the envelopes and their content.

Given the long-term local complications, infrequent but serious, due to leakage of silicone gel, we were naturally led to filling our implants with another filler: carboxy methyl cellulose

dissolved in saline.

After human application during 15 years, we can say that the CMC gel filling represents a significant advance for the reliability of breast implants and the safety of our operated patients.

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