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Chemical incompatibility between polymerizing HEMA and rubber balloons used for selective endovascular treatment of intracranial aneurysms

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Permanent selective occlusion by detachable balloons with parent vessel preservation is considered to be the endovascular treatment of choice of intracranial aneurysms. It has been proposed that replacement of contrast material within the balloon with a polymerizing substance will eliminate balloon deflation. Despite this solution, our clinical experience with polyisoprene rubber balloons shows that deflation can still occur when the balloons are filled with poly(2-hydroxyethyl methacrylate). Experimental data are presented that demonstrate the chemical incompatibility between hydroxyethyl methacrylate (HEMA) and polyisoprene rubber. The resulting degradation of the polyisoprene rubber accounts well for balloon failure. The *in vitro* behaviour of silicone balloons and of a new HEMA sponge formulation to fill the balloons are compared.

1. Introduction

In past years, selective embolization of intracranial aneurysms by using inflatable and detachable balloons has been regarded as suitable in therapeutic angiography [1–3]. Balloons made of natural polyisoprene rubber or of silicone have been used either to fill up the whole aneurysm pouch or only to close the aneurysm neck. Early deflation was found when balloons were inflated with an aqueous solution of iodine containing contrast medium only [1]. In order to avoid such deflation, polymerizable acrylic monomers have been used to inflate the balloons and to secure shape and size by polymerization after setting the inflated balloons into the aneurysm pouch. When the polymerization is completed, the balloon can be detached by pulling out the catheter. Because of its hydrophilicity and of its ability to polymerize easily to form biocompatible and swellable hydrogels, hydroxyethyl methacrylate (HEMA), has been considered as a suitable filler for balloons [4, 5]. Furthermore, the resulting polymer can be made radio-opaque to X-rays by mixing with iodine contrast medium. However, after successful setting of polyisoprene rubber balloons filled with poly(2-hydroxyethyl methacrylate) in the aneurysm pouch, a rather large number of aneurysm repermeations resulting from a volume decrease of the polymer plug and an early decrease of the balloons X-ray opacity have been observed at Lariboisière Hospital in Paris.

In order to identify the origin of these two unexpected features, we decided to carry out *in vitro* investigations of the polymerization of HEMA in polyisoprene rubber and in silicone balloons under the conditions normally used in therapy. HEMA is a water soluble acrylic monomer which can be readily polymerized in aqueous media and at body temperature by using oxidation–reduction reactions to generate the radicals necessary to initiate the polymerization. Bifunctional ethyleneglycol dimethacrylate (EGDMA), which is normally present as a trace impurity in commercially available HEMA, can be added to the polymerization mixture in known amounts in order to crosslink poly(2-hydroxyethylmethacrylate) chains, which leads to insoluble hydrogels [6–8]. The morphology of the resulting hydrogels depends on the composition of the polymerization mixture and especially on the proportion of water [6, 9]. Homogeneous hydrogels (which will be named pHEMAh), are obtained for water contents in the 0%–50% vol/vol range whereas heterogeneous spongy hydrogels (pHEMAs), are formed when the water content is larger than $\sim$ 55%. As far as aneurysm therapy is concerned, only pHEMAh have been used to secure the balloons. However, the use of pHEMAs spongy material is of great potential interest because the corresponding monomer formulation is much less viscous than the formulation used to make homogeneous poly(2-hydroxyethyl methacrylate)

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hydrogels. Thus, it allows injection through small-diameter catheters as requested for the treatment of intracerebral lesions.

In this paper, the results of a comparative *in vitro* study of both pHEMAh and pHEMAs formulations are reported with respect to the requirements for balloon securing and aneurysm obturation.

2. Materials and methods

2.1. Basic components

1. 2-hydroxyethylmethacrylate (HEMA) was purchased from Polysciences, Warrington, USA. Gas chromatography (GC) analysis was used to check the purity of the supplied compound which was found to be 99% HEMA and 1% residual ethyleneglycol dimethacrylate.

2. Cross-linking agent: ethyleneglycol dimethacrylate (EGDMA), MW 200, was also obtained from Polysciences, Warrington, USA, as 99.9% EGDMA according to GC.

3. Initiator system: the initiator system was prepared from a crystalline ferrous ammonium sulphate (FAS), supplied by Interventional Therapeutics Corporation, San Francisco, USA or Prolabo, Paris, France and a 3% hydrogen peroxide solution obtained from Pharmacie Centrale des Hôpitaux de Paris. 50 mg FAS were dissolved in 1 ml ion-free sterile water immediately before the preparation of the mixtures to be polymerized.

4. Iodine contrast media: we used in our experiments either a non-ionic, slightly hyperosmolar contrast medium, iopamidol (Iopamiron® 300 mg/ml iodine, Scherring, Lys-Lez-Lannoy, France), or a non-ionic, roughly iso-osmolar contrast medium, metrizamide (Amipaque® 180 mg/ml iodine, Nycomed, Paris, France). In order to obtain a sufficient contrast of the balloon through the skull the proportion of contrast medium in the polymerizing mixture has to reach 30% (vol/vol) using contrast media with 300 mg/ml iodine.

5. Balloons: two types of valve-balloon were used, polyisoprene rubber balloons of various wall thicknesses (Elastotechnics, Paris, France) with a polyisoprene rubber valve mechanism [10] and silicone valve-balloons (Heyer Schulte Corporation, USA, Ingenor, Paris, France) [11, 12].

2.2. Preparation of hydrogels and sponges

2.2.1. Poly(2-hydroxyethylmethacrylate) hydrogels

Two mixtures with different compositions (wt/wt) were prepared: (a) HEMA monomer and EGDMA 35.8%, hydrogen peroxide 14.2%–contrast medium (iopamidol or metrizamide) 50%, (b) HEMA monomer and EGDMA 51.2%, hydrogen peroxide 20.2%–contrast medium (iopamidol) 28.6%.

In these two formulations, EGDMA represents 1% by volume of HEMA monomer. Polymerizations of these mixtures were initiated by introducing a solution of ferrous ammonium sulphate (FAS) into the monomer mixtures (5% to 8% vol/vol) just before introduction into the balloons.

2.2.2. Poly(2-hydroxyethylmethacrylate) sponges

The new formulation we have proposed was HEMA monomer and EGDMA–20.6%, hydrogen peroxide 8.1%, sterile water 41.4%–contrast medium (iopamidol) 29.9% (wt/wt).

EGDMA represents 2% by volume of HEMA monomer. If we consider the water content of contrast medium (40%), the whole water content in the mixture, including hydrogen peroxide, is 61.4%. Monomer mixtures with more than 55% total water yield spongy materials with open porosity in the range of 50 μm [9].

2.3. Methods

Balloons were inflated through a 1-French-catheter (0.20 mm i.d., 0.33 mm o.d.), after mixing the various components together and they were allowed to polymerize in saline at 37 °C.

Polyisoprene rubber balloons and silicone balloons were inflated with various HEMA formulations for making hydrogels or sponges. The compositions were selected in order to yield homogeneous hydrogels and to fulfil the specific requirements as much as possible. The fate of the balloons immersed in normal saline was monitored for a 3 month period. Their volume was evaluated by measuring the length and the width of the balloons considering a cylindrical form.

Ultraviolet spectrophotometric analyses were performed with a Perkin Elmer apparatus.

Fourier transform infrared (FTIR) spectra were recorded with a Perkin Elmer 1760 spectrophotometer.

3. Results and discussion

The inflation of the balloons was performed through the catheter after mixing the monomers, the initiator and the opacifying agent. Before polymerization the pHEMAh mixture was viscous and not easy to inject into the small delivery catheters used in embolization. The fluid pHEMAs mixture was easily injected.

The results of the polymerization in the balloons are summarized in Table I. Polyisoprene rubber balloons filled with poly(2-hydroxyethyl methacrylate) formulations, whether for hydrogel or sponge, were all damaged. A few days after filling the balloons with the monomer mixture, polyisoprene rubber walls broke and presented longitudinal or circular fractures. In contrast, silicone balloons did not show any significant changes of membrane aspect.

Both size reduction and membrane destruction were observed in the cases of polyisoprene rubber balloons. Fig. 1a shows a polyisoprene rubber balloon filled with pHEMAh after polymerization and standing for 48 h at 37 °C in saline. Fig. 1b shows a polyisoprene rubber balloon filled with pHEMAs formulation after 48 h in saline at 37 °C. As in the case of pHEMAh, polyisoprene rubber balloons exhibited

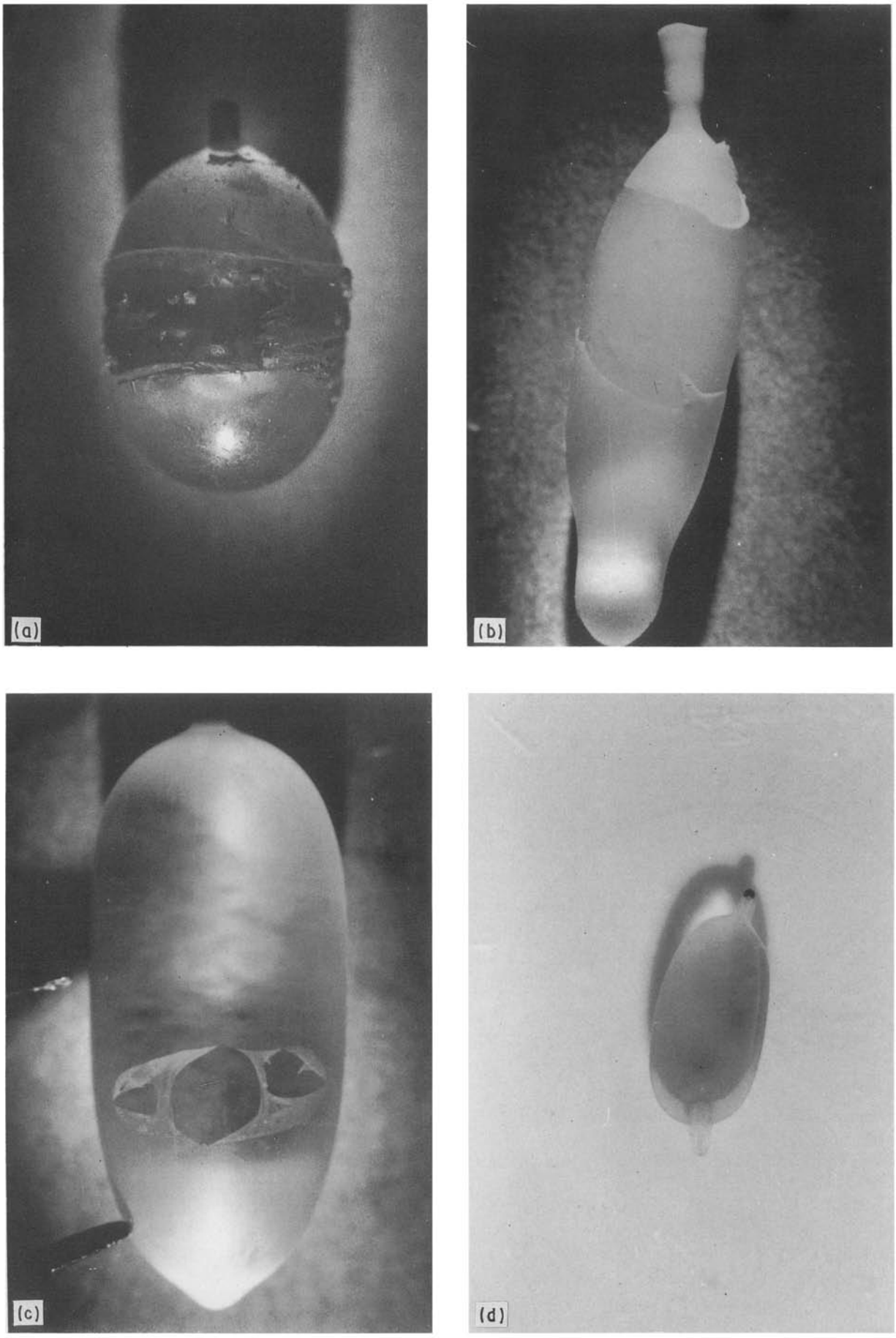

Figure 1 Visual aspects of polyisoprene rubber balloons inflated with (a) the polymerizing pHEMAh formulation and (b) a polymerizing pHEMAs formulation, and allowed to stand for 48 h in saline at 37 °C. (c) Visual aspect of a polyisoprene rubber balloon inflated with a mixture of ferrous ammonium sulphate and hydrogen peroxide and allowed to stand for 1 week in saline at 37 °C. (d) Visual aspect of a silicone rubber balloon inflated with a mixture of pHEMAh + low osmolarity iodine contrast medium (Iopamidol 300 mg iodine/ml) and allowed to stand for 2 months in saline at 37 °C.

TABLE I Evolution of latex and silicone balloons filled with pHEMA (hydrogel and sponge-like polymer)

Balloons nature	Contents	Degradation (wall rupture)	Volume variations	Delays (months)
1 Latex	HEMA hydrogel/iopamidol	Yes	Deflation (− 40%)	2
2 Latex	HEMA hydrogel/iopamidol	Yes	Deflation (− 39%)	2
3 Latex	HEMA hydrogel/metrizamide	Yes	Deflation (− 33%)	2
4 Latex	HEMA sponge/iopamidol	Yes	Deflation (− 63%)	2
5 Silicone	HEMA hydrogel/iopamidol	No	Inflation (+ 31.8%)	2
6 Silicone	HEMA hydrogel/metrizamide	No	Deflation (− 11.1%)	2
7 Silicone	HEMA sponge/iopamidol	No	Deflation (− 31%)	2

deflation and membrane breakings. In contrast, silicone balloons presented no rupture; however, those filled with pHEMAs showed deflation.

As far as polyisoprene rubber balloons are concerned, the origin of the degradation of the polyisoprene membrane is directly related to the presence of ethylenic double bonds in the repeating units. Indeed, the polyisoprene rubber which was used to make balloons was based on natural polyisoprene. It is well known in polymer chemistry that insaturated elastomers can undergo chain grafting when in contact with acrylic monomers and initiators. In the particular case of latexes used, grafting of HEMA to polyisoprene chains affected the mechanical properties and caused swelling because of the hydrophilicity caused by poly(2-hydroxyethylmethacrylate) grafts. A polyisoprene rubber balloon filled with a monomer-free ferrous ammonium sulphate and hydrogen peroxide aqueous solution showed an early degradation of the internal layers but the balloon remained inflated (Fig. 1c). Deflation occurred a few days later because of osmotic exchanges. In the presence of HEMA, the same mixture led to a dramatic degradation of the polyisoprene rubber. Infrared spectrophotometric analysis of initial polyisoprene rubber and damaged polyisoprene rubber, showed absorption at 1715 cm^{-1} typical of C = O groups, thus demonstrating oxidation of double bonds. Grafting of acrylic monomers was not possible in the case of saturated silicone balloons, thus explaining that this type of balloon was not degraded and presented no leakage of iodine contrast medium (Table II).

Although similar effects occurred for both pHEMAh and pHEMAs fillings, the pHEMAs formulation seemed to be better adapted to the prerequisites of balloon inflation. The main advantages of this formulation were the high fluidity of the mixture before polymerization due to the water content and the flexibility of the final mass. Indeed, fluidity allows easier injection into the small catheter with respect to formulation for pHEMAh, and the flexibility is of interest for the treatment of intracerebral lesions as the whole mass is less traumatic and absorbs better pulsatory arterial shocks. These two features are of great interest with respect to endovascular embolization of intracerebral aneurysms. However, such formulation which contains more water has not yet been applied because of degradation, in the case of natural rubber, and because of excessive semi-permeability, in the case of silicones.

TABLE II Silicone balloons. Contrast media and residual HEMA monomer leakages out of pHEMA (hydrogel and sponge-like polymer) in ultraviolet spectrophotometric analysis of normal saline (% by initial volume; days 14, 21 and 36 after balloon filling)

	D14	D21	D36
Gel			
Iopamidol leakage (%)	0.3	1	2.5
HEMA leakage (%)	3.5	3.5	3.5
Sponge			
Iopamidol leakage (%)	1	2	2
HEMA leakage (%)	3	13	13

In spite of the difference in membrane resistance between polyisoprene rubber balloons and silicone balloons, for both types, volume variation was observed to various extents depending on the experimental conditions (Table I). For poly(2-hydroxyethyl methacrylate) hydrogels, size reduction reached 40%, whereas the size of the balloons with spongy poly(2-hydroxyethyl methacrylate) was reduced by 63%. Hydrogel deflation can be explained by the leaching of contrast molecules and residual HEMA monomer out of the polymer plug after membrane breaking. However, we have found that size reduction was mostly due to osmotic exchange of matter through the membranes regardless of their chemical natures. This was ascertained by ultraviolet spectrophotometric analysis of the saline media, because the opacifying agents absorbed ultraviolet light (Table III). The osmotic origin of the size changes of the balloons which were allowed to age in saline during and after polymerization was conclusively shown by considering the effects of modifications of the osmolarity of the surrounding aqueous medium on the size of silicone balloons. With hyperosmolar contrast media (iopamidol, 680 mOsmol) silicone balloons inflated in normal saline because of the uptake of water indispensable to decrease the chemical potential up to that of the surrounding saline solution (Fig. 1d). Inflation as high as 31% was observed. On the contrary, when almost iso-osmolar contrast medium (metrizamide 300 mOsmol kg^{-1}) was used, silicone balloons became slightly deflated. These findings agree well with the fact that volume stability of a silicone balloon filled with poly(2-hydroxyethyl methacrylate) was mentioned as possible only with a slightly hyperosmolar contrast media such as metrizamide 200 or 220 mg ml^{-1} iodine [4, 11]. Such solvent exchange

TABLE III Latex balloons. Contrast media and HEMA monomer leakages out of pHEMA (hydrogel and sponge-like polymer) in ultraviolet spectrophotometric analysis of normal saline (% by initial volume; 3 h and days 2, 3, 7 after balloon filling)

	D0 (3 h)	D2	D3	D7
Hydrogel				
Iopamidol leakage (%)	0	2.5	11	29
HEMA leakage (%)	0.04	2	2	2
Sponge				
Iopamidol leakage (%)	3	14	25	44
HEMA leakage (%)	6	8	8	8

through the polymer membrane appeared dramatic in the case of diluted pHEMAs formulations. Indeed, hypo-osmolarity led not only to rather large size contraction but also to formulation modifications. The transfer of water from the polymerizing medium to the surrounding saline solution resulted in a polymerizing mixture evoluting from the sponge-generating formulation to the homogeneous hydrogel-generating one.

4. Conclusion

Chemical incompatibility between polyisoprene rubber balloons and poly(2-hydroxyethyl methacrylate) homogeneous hydrogels currently used for intracranial aneurysm embolization accounts well for the critical problems observed in clinical applications. Size changes are likely to be observed if osmolarity of the inflating medium is not adapted to that of body fluids. Furthermore, the use of radically polymerized acrylic monomers such as HEMA and EGDMA must be excluded with polyisoprene rubber balloons because of the dramatic consequences of the side reactions involving polyisoprene insaturations. In spite of their better behaviour with respect to poly(2-hydroxyethyl methacrylate) hydrogels, silicone balloons cause many problems too: excessive semipermeability, low elasticity, requirement of larger delivery catheter and finally high cost. From a better understanding of the behaviour of balloons and of the filling materials, one can expect to find a new type of balloon exhibiting suitable elasticity, impermeability, chemical inertness and biocompatibility. With such characteristics, the problems of selective endovascular treatment of intracranial aneurysms could be solved and sponge-generating HEMA formulations could be used.

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