A chemical evolution of NVP-containing VIPAR-family 3D polymer gel dosimeters – a brief overview

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Abstract. NVP-containing three-dimensional polymer gel dosimeters for radiotherapy dosimetry have been developed for more than 20 years. There have been 11 main modifications of the originally proposed VIPAR polymer gel dosimeter that altogether have amounted to 12 gel dosimeter formulae. This communication is to summarise the main chemical changes made to the VIPAR dosimeter over these years of research. The newest NVP-polymer gel dosimeters are also introduced.

1. Introduction
Over the last 25 years, three-dimensional (3D) radiotherapy dosimetry has flourished and offers a range of 3D high-resolution dosimeters [1], which can be divided into two classes: (1) polymer gels and (2) radiochromic dosimeters. Polymer gel dosimeters act upon conversion of vinyl monomers into a polymer and crosslinked polymer, whereas in radiochromic dosimeters, a colour is induced by conversion of a dye or other compound upon irradiation. Examples of polymer gel dosimeters include: BANG, PAG, MAGIC, MAGAT, PAGAS, PAGAT, NIPAM, VIPAR, VIP, VIC, PABIG, PABIGnx, and deformable Aquajoint®-based gels [2-19]; however, in the case of radiochromic dosimeters, the following can be mentioned: Fricke-based gels [20], plastic dosimeters [21], deformable FlexyDos3D [22], and radiochromic gels including leuco dye micelle gels [23-25] and leuco dye and tetrazolium salt Pluronic gels [26, 27].

Among these dosimeters are the VIPAR-family gels, which have undergone a range of chemical alterations resulting in 12 N-vinylpyrrolidone-containing chemical formulae. This communication is to briefly report on the development of VIPAR gels.

2. An overview of NVP-containing dosimeters
In Figure 1, a scheme of VIPAR-family gel dosimeter evolution is shown. The main events of this evolution are presented below. The first polymer gel dosimeter with N-vinylpyrrolidone (NVP) was proposed in 1999 by Pappas et al [16] and was called VIPAR. In addition to NVP, it also contained 4% N,N'-methylenebisacrylamide (MBA or Bis) and 5% gelatine. The composition had to be saturated with argon for elimination of oxygen, which was common to all polymer gel dosimeters at that time (mostly saturated with nitrogen or argon). This allowed for the radical polymerization and crosslinking of NVP and MBA under exposition to ionizing radiation. The main advantage of VIPAR was a high dynamic
dose range and saturation at doses greater than 200 Gy. In turn, its main disadvantage was a relatively high dose threshold (assessed in different publications from approximately 2 to 13 Gy). VIPAR exhibited a low dose sensitivity (0.04–0.095 1/(Gy × s)); however, this feature and the high dynamic dose range allowed for its use in measurements of radiation dose distributions for high dose gradients; for instance, in HDR (192Ir) brachytherapy or in CyberKnife dosimetry studies [14].

The problem of the VIPAR’s high dose threshold was solved by doubling the concentration of NVP; the gelatine concentration had to be increased to 7.5% to maintain proper stiffness of the dosimeter. This gel dosimeter was named VIPAR\textsuperscript{d}, where ‘d’ denotes the double concentration of NVP [28]. The introduction of normoxic gel dosimeters and thus elimination of the necessity of oxygen removal from polymer gel dosimeters [6] led to the proposition of normoxic VIPAR\textsuperscript{nd}, where ‘nd’ denoted normoxic-double [9]. The oxygen scavengers of ascorbic acid (0.007%) and copper sulfate pentahydrate (0.0008%) were used, which facilitated manufacturing of the dosimeters. In turn, VIPAR\textsuperscript{nd} (called also VIP) was commonly used in radiotherapy dosimetry research [14, 29]. The highest dose sensitivity obtained for VIP was equal to 0.0888 1/(Gy × s), whereas the linear dose range was equal to ~0.5–35 Gy and the dynamic dose range was equal to ~0.5–120 Gy (1.5 T magnetic resonance imaging [MRI]) [9].

![Figure 1](image.png)

**Figure 1.** Scheme illustrating the development of VIPAR-family polymer gel dosimeters. The normoxic dosimeters of the highest dose sensitivity are marked in blue. The dose sensitivities were taken from the following publications: VIPAR [9, 16, 28, 30-32]; VIPAR\textsuperscript{d} [28]; VIP [9, 11, 14, 33]; modified VIPAR [15]; VIPET [12, 15, 34]; VIPET \textsuperscript{1v} and \textsuperscript{2v} [35]; VIC [11]; AQUAJOINT gel [36]; VIPET\textsuperscript{aqe} [12]; VIC-T [37]; and VIP3-Pluronic [38].

Papadakis et al and Papoutsaki et al [15, 35] examined the impact of increasing gelatine concentration in VIPAR and showed that it can be modified to a normoxic gel dosimeter using tetrakis(hydroxymethyl)phosphonium chloride (THPC) following the proposition of De Deene et al [5]. Thus, the VIPET gel dosimeter was prepared with 4% MBA, 4% NVP, 7% gelatine, and 5 mM THPC,
as proposed previously [39]. VIPET was examined by 1.5 T MRI with some scanning protocols, which lead to dose sensitivities of 0.035, 0.048, and 0.0761 1/(Gy × s). The dose threshold was equal to 2 Gy and the linear dose range was 2-32 Gy (dynamic dose range: ~100 Gy). A reason for this high dose threshold may have been the lack of optimisation of the THPC concentration in VIPET. The next step in VIPET optimisation was to increase the NVP concentration to 8%, as was done previously [28]. This impacted the VIPET dose sensitivity in comparison with VIPET with 4% NVP: 0.063 and 0.059 1/(Gy × s), respectively (1.5 T MRI, PHAPS 32-echo train) [35]. Additionally, VIPET gels were reported to be unstable following preparation and irradiation; however, the dose sensitivity remained unchanged over time after irradiation.

The next significant step in the evolution of VIPAR-family dosimeters was a VIC (VIPARCT) polymer gel [11], comprising 17% NVP, 8% MBA, 12% t-BuOH, 7.5% gelatine, 0.007% ascorbic acid, 0.0008% CuSO4·5H2O, and 0.02% hydroquinone. The dosimeter exhibited the highest dose sensitivity (0.171 1/(Gy × s), 0.47 T NMR) among all NVP-gel dosimeters (on a par with VIC-T, see below). The VIC performed better than VIP using X-ray computed tomography as a readout method with a dose sensitivity (0.397 HU/Gy) 1.5-fold higher than that of VIP.

Takanashi et al [36] and Maeyama et al [12] proposed a flexible matrix for NVP-containing gel dosimeters of relatively high dose sensitivity (0.16 1/(Gy × s)). However, this composition requires more detailed analysis.

A substitution of copper sulfate pentahydrate and ascorbic acid with THPC was also examined for the VIC dosimeter [37]. The study resulted in a VIC-T dosimetric composition of analogous to VIC dose sensitivity, a dose threshold of 0.5 Gy, a dynamic dose range of 0.5–50 Gy, and a linear dose range up to 20 Gy (30 Gy for VIC) (derived from 0.47 T NMR measurements). The dose response of VIC-T was independent of the radiation dose rate, type, and energy of radiation for 6 and 15 MV photons and 12 MeV electrons, which is an improvement with respect to VIC, which showed a different dose response for 6 MV photons compared with 12 MeV electrons and 15 MV photons. A feature of VIC-T is its improved/altered thermal properties with respect to other NVP-containing gel dosimeters, as it does not melt in the temperature range of about 0-80°C [37]. The thermal properties of VIC-T are discussed elsewhere [37].

**Table 1.** Comparison of the basic calibration properties of NVP-containing normoxic gel dosimeters of the highest dose sensitivities among all VIPAR-family gels.

| Dosimeter     | Dose sensitivity* [1/(Gy × s)] | Intercept [1/s] | R²   | Threshold dose [Gy] | Linear dose range [Gy] | Dynamic dose range [Gy] |
|---------------|-------------------------------|----------------|------|---------------------|------------------------|------------------------|
| VIP           | 0.089                         | 3.447          | n.d. | 0.5–1.5             | <1.5–35                | <1.5–120                |
| VIC           | 0.171                         | 1.783          | 0.999| 0.5                 | 0.9–30                 | 0.5–50                  |
| VIC-T         | 0.176                         | 1.049          | 0.998| 0.5                 | 0.5–20                 | 0.5–50                  |
| VIP3-Pluronic | 0.101                         | 1.249          | 0.999| 0.5                 | 0.5–30                 | 0.5–>50                 |
| VIPETqua      | 0.16                          | 1.85           | n.d. | n.d.                | n.d.                   | n.d.                   |

*The highest dose sensitivity is presented. Note that the dose sensitivity may be affected by the type of magnetic resonance imaging and scanning protocol. The calibration parameters are given for different measurements set-up (see references in Figure 1).

A substitution of the natural polymer-based physical gel matrix of gelatine with a synthetic co-polymer physical gel matrix of Pluronic F-127 for NVP-containing polymer gel dosimeter was also proposed [38], which led to the VIP3-Pluronic dosimeter with a dose sensitivity of 0.101 1/(Gy × s), a linear dose range of 0.5–30 Gy, and a dynamic dose range of 0.5–50 Gy (0.47 T NMR). The thermal stability of this gel was improved at temperatures above room temperature due the inclusion of the Pluronic matrix.
with respect to the NVP-containing polymer gels with gelatine and ascorbic acid and copper sulfate pentahydrate as oxygen scavengers (thermal stability of VIP3-Pluronic based on T_gel derived from differential scanning calorimetry, 4.4–56.7°C and VIP, 0–26°C [38]). Table 1 illustrates the main properties of VIPAR-family normoxic gel dosimeters with the highest dose sensitivities, which have been considered promising for further studies.

3. Conclusions
This work summarises a 20-year evolution of NVP-containing 3D polymer gel dosimeters. The NVP monomer differentiates this family of gel dosimeters from other 3D dosimeters.

The first proposed VIPAR polymer gel dosimeter underwent several alterations of its composition including changes in monomer concentrations while maintaining the main monomers (NVP and MBA) in each new composition, substituting the gelatine matrix with other matrices, and the addition of other substances such as oxygen scavengers or co-solvents that allowed for alterations of its mean features. Thus, improvements in dose sensitivity were obtained and the new normoxic gels are easier to prepare. Some of the alterations have also led to improvements and changes of the thermal properties of VIC-T and VIP-Pluronic dosimeters. The newest promising normoxic NVP-containing polymer gel dosimeters of the highest dose sensitivity are VIP, VIC, VIC-T, VIP3-Pluronic, and VIPETaq.

4. References
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