



Drug delivery in thermo-responsive silicone catheters by grafting of N-vinylcaprolactam using gamma radiation

Manuel U. Ramirez-Fuentes, Lorena Duarte-Peña , Emilio Bucio , Departamento de Química de Radiaciones y Radioquímica, Instituto de Ciencias Nucleares, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, 04510 Mexico, Mexico

Address all correspondence to Lorena Duarte-Peña at lorena.du.pe@gmail.com and Emilio Bucio at ebucio@nucleares.unam.mx

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Abstract

Radiation-induced graft polymerization of poly(N-vinylcaprolactam) onto silicone catheters by direct irradiation method was studied. The effects of the irradiation dose, as well as the monomer concentration, on the grafting efficiency were studied. The conditions for achieving maximum grafting yield were observed at 30% of monomer concentration in toluene at 50 kGy. The graft polymerization was examined by different characterization methods, including measurements such as thermogravimetric analysis, infrared, water contact angle, and swelling. The temperature-responsive behavior of smart grafted copolymer was studied by swelling at different temperatures. Differently from pristine silicone catheter, the N-vinylcaprolactam-grafted catheters were able to load vancomycin and sustain the release for 30 h.

Introduction

Urinary catheters are one of the most widely used medical devices since are assistants for the treatment of various procedures such as surgeries, chemotherapy, and kidney tests.^[1,2] These can be intermittent or indwelling, the first is used each time that it is necessary to drain the bladder, while the last is left in the bladder and helps to collect the urine. The employment of indwelling catheters is one of the most common causes of nosocomial infections; about 20% of bacteremia in the intensive care unit and 50% in long-term care centers are due to these devices. In addition, it is estimated that urinary catheters are responsible for between 70 and 80% of urinary infections, known as catheter-associated urinary tract infections (CAUTI). These infections are generally produced by the formation of bacterial biofilms, whose conformation protects bacteria from antimicrobials and host defenses, making them highly resistant.^[3]

Latex and silicone urinary catheters are commonly used, due to these minimize urethral trauma. However, silicone catheters are less prone to blockage, making them ideal for indwelling treatments.^[4] Silicone is a biocompatible, hypoallergenic synthetic polymer with excellent mechanical properties and chemical resistance, wished characteristics for its application in the manufacture of medical devices.^[5,6] The problem with silicone devices is that since it is a hydrophobic material, it suffers from the adhesion of bacteria and the formation of biofilms. To mitigate this problem, antimicrobial coatings have been developed that prevent proliferation, but it continues in research.

One of the ways to provide the surface with antimicrobial properties is through surface modification with stimulus-responsive polymers that allow the loading and release of antimicrobial drugs. Stimulus-responsive polymers are polymeric

materials that change their structure in the presence of an external stimulus such as temperature or pH. Poly(N-vinylcaprolactam) (PNVCL) is a biocompatible and thermo-responsive polymer that has a lower critical solution temperature (LCST), that is, its structure is less hydrophilic at temperatures higher than its critical temperature (32–34°C).^[7] Due to its critical temperature range, the PNVCL is a promising material for drug delivery under physiological conditions.^[8,9] This material has been used for the synthesis of injectable hydrogels to encourage the growth of cartilage tissue, showing promising results in *in vitro* tests.^[10] Furthermore, NVCL can copolymerize to form micelles or hybrid gels with a high potential for drug release.^[11,12] For example, Singh et al. synthesized amphiphilic block copolymers of N-acrylamidohexanoic acid and NVCL to form micelles, which allow the encapsulation and delivery of hydrophobic drugs.^[13]

Gamma radiation is a high-energy radiation that produces the matter ionization. When a polymer is irradiated, radicals are created along its chain that act as growth points for the graft. The formation of grafts using gamma radiation as an initiator has the advantage of reproducibility, not requiring high temperatures, and avoiding material contamination since it does not need initiators.^[14,15] Due to the above, the use of gamma radiation for the development of biomaterials has increased in recent years, reporting materials used for dressing, drug delivery systems, tissues engineering, and biosensors.^[16]

This work proposes the modification of silicone catheters using gamma radiation to graft PNVCL, which is a thermo-responsive polymer that gives the catheter the ability to load and release a drug, which may reduce infection incidences in this device. The model drug was vancomycin, an antibiotic against gram-positive bacteria such as *Staphylococcus aureus*,

Streptococcus pyogenes, and *Streptococcus pneumoniae*. Vancomycin is employed for serious infection treatments and bacteria resistant to other antibiotics, such as methicillin-resistant *Staphylococcus aureus*.^[17,18] *S. aureus* is one of the bacteria that most cause infection in catheters, and vancomycin is an antibiotic that has high activity against these bacteria.

Materials and methods

Materials

Silicone catheters with a diameter of 5 mm and thickness of 2 mm were obtained from China and washed with ethanol for 8 h and then dried under reduced pressure. N-vinylcaprolactam was purchased from Sigma Aldrich (USA) and distilled under reduced pressure before use. Toluene and methanol were from J.T. Baker (Mexico) and used as received. Distilled water was used for the reaction and analysis. Vancomycin was acquired from Fagron (Colombia) and used as received.

Grafting of SRcat-g-NVCL

Grafting of N-vinylcaprolactam onto silicone catheter, SRcat-g-NVCL was synthesized by direct irradiation method using a ⁶⁰Co γ-ray source.

The glass ampoules were prepared containing a silicone catheter (2.5 cm length) with a solution of monomer concentration in toluene (from 5 to 50% of NVCL vol.%) or methanol (between 10 and 60% of NVCL vol.%) at different doses and dose rate $\approx 8.5 \pm 0.5$ kGy/h. Grafting was evaluated by using Eq. 1:

$$\text{Grafting (\%)} = ((W_g - W_o) / W_o) * 100, \quad (1)$$

where W_o and W_g are the initial and grafted weight of the films, respectively.

Characterization

For determination of the swelling limit, the catheters were immersed into distilled water at different times, the excess of solution on the catheter's surface was wiped off with paper, and the swollen catheters were weighed. The swelling yield of the samples was calculated by Eq. 2.

$$\text{Swelling (\%)} = ((W_s - W_d) / W_d) * 100, \quad (2)$$

where W_s and W_d are the weights of the swollen and initial films, respectively.

The contact angle was measured at room temperature using a goniometer (DSA 100, Krüss GmbH, Germany) and distilled water. Before the measure, the catheters were flattened until they reached a homogeneous surface and dried. The contact angle was recorded using the computer software at 0 and 5 min. Each measurement was conducted in triplicate.

The lower critical solution temperature (LCST) was evaluated with distilled water swelling measurements at temperatures between 25 and 36°C, where the LCST was defined as the

inflection point of the swelling vs. temperature plot (Boltzmann function fitting).

FTIR-ATR (attenuated total reflection) spectra of the starting and modified SR catheters were analyzed using a Perkin-Elmer PARAGON 500 spectrometer (USA), in the horizontal attenuated reflectance mode, and a SeZn glass was used as contact with the sample surface, and 16 scans.

Thermogravimetric analysis (TGA) measurements were carried out on a TA instruments TGA Q50 (USA) ramping from 25 to 800°C at a heating rate of 10°C/min under a nitrogen atmosphere.

Vancomycin loading and release

Vancomycin loading was performed in grafting catheters with 3, 10, and 18% for PNVCL. The dried catheters were immersed in 3 mL of 2 mg/mL vancomycin solution at 25°C. The amount of load was calculated through UV absorbance measurement at 275 nm employing a calibration curve, Eq. 3 with $r^2 = 0.999$.

$$\text{Absorbance} = 2.15[\text{Vancomycin concentration (mg/mL)}] \quad (3)$$

Vancomycin release was performed into phosphate buffer at pH 7.4 and 37°C with constant mechanical stirring. The release profiles were monitored by UV spectrometry at 270 nm. The concentration of the released drug was calculated using a calibration curve (Eq. 4, $r^2 = 0.999$). Measurements were conducted in triplicate.

$$\text{Absorbance} = 3.20[\text{Vancomycin concentration (mg/mL)}] \quad (4)$$

A SPECORD 200 PLUS brand spectrophotometer from Analytikjena (Germany) was used for the measurements.

Results

Grafting PNVCL onto silicone catheters (SRcat-g-PNVCL)

The modification of the silicone catheters was performed using the direct irradiation method, in which the monomer and the matrix to graft are irradiated simultaneously. When silicone comes into contact with radiation, it forms different radicals (Fig. 1(a)), of which radical IV is the most stable.^[19-21] The variables that interfere in this process are the solvent, the monomer concentration, and the irradiation dose.

The solvent must allow the interaction between the monomer and the matrix and a total monomer dissolution. Toluene and methanol were tested as solvents; toluene allowed a greater diffusion of the monomer into the matrix, which resulted in an increase in the PNVCL grafting percentage, as shown in Fig. 2(b). Figure 2(b) also shows the behavior of the PNVCL grafting in relation to the monomer concentration. When using toluene, an increase in the grafting percentage was observed until it stabilized after a 30% v/v concentration in the conditions used. This behavior occurs due to the gel effect, which consists of a self-acceleration of polymerization that is

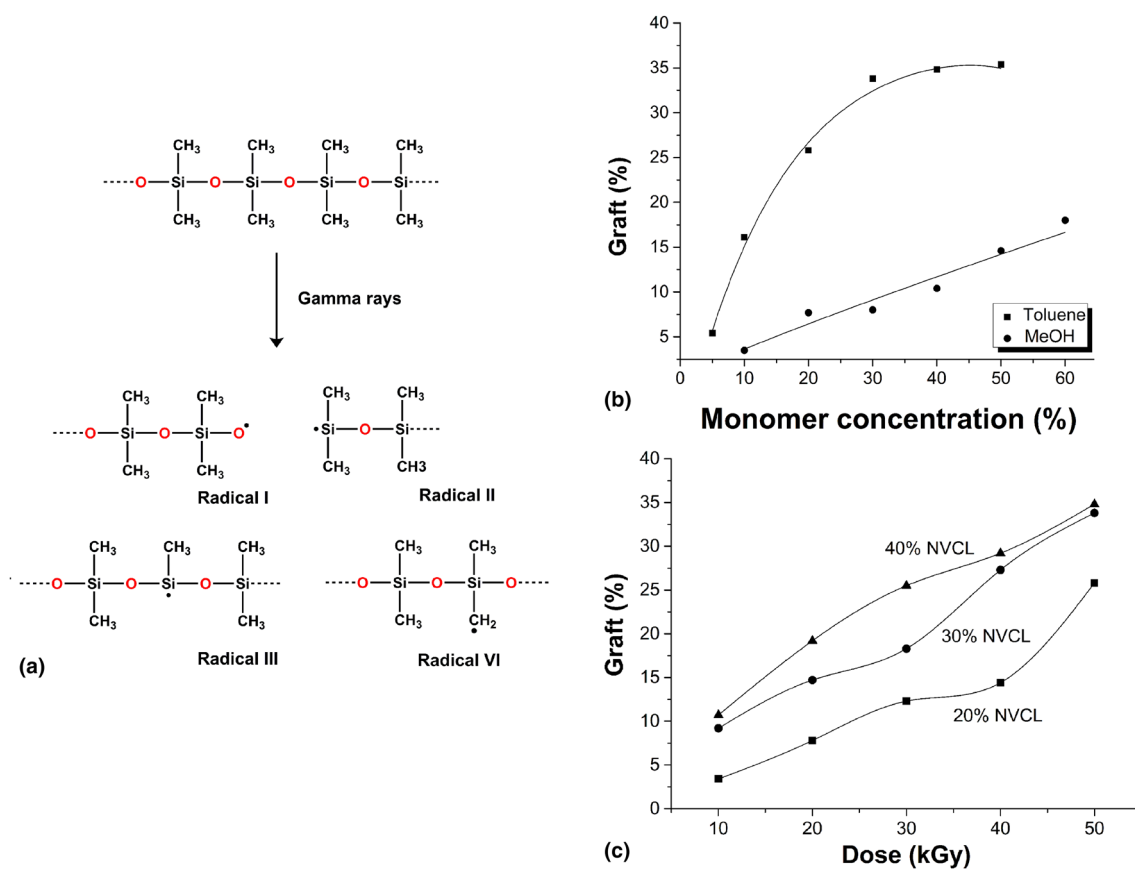


Figure 1. (a) Radical formation by silicone irradiation with gamma rays; (b) Grafting as function of monomer concentration in toluene and MeOH, dose 50 kGy, dose rate 8.5 ± 0.1 kGy/h; and (c) Grafting as function of dose at different monomer concentrations 20%, 30%, and 40% in toluene, dose rate 8.5 ± 0.1 kGy/h.

produced by an increase in the viscosity of the medium that makes termination reactions difficult, resulting in the formation of homopolymer gels rather than grafting.^[22] Figure 3(c) shows the irradiation dose effect on the grafting percentage when using different concentrations (20, 30, and 40% v/v); in all cases, the graft percentage increased with increasing dose; it is also observed that at high doses of 40 and 50 kGy, there are no significant differences in the grafting percentage for 30 and 40% monomer concentrations.

Characterization

The material characterization was carried out by different assays. Initially, infrared spectroscopy was used to determine the presence of the functional groups of the matrix and the grafting monomer. Figure 2(a) shows the spectrum of pristine silicone catheters, which presents a band at 2964 cm^{-1} corresponding to the C-H stretching of the methyl groups, bands at 1257 cm^{-1} of the Si-C stretching, as well as two pronounced bands at 997 and 820 cm^{-1} of Si-O-Si stretching and Si-(CH₃)₂ bending.^[23] The spectrum of PVNCL is also shown, which presents characteristic bands at 2923 cm^{-1} of C-H stretching, as well as bands own of the amide at

1625 cm^{-1} and of C-N stretching at 1479 cm^{-1} .^[24] The silicone catheters modified with PNVCL presented spectra that present the characteristic bands of both silicone and PNVCL. The amide and C-N stretching bands increased their intensity with increasing the PNVCL grafting percentage, which confirmed the grafting formation.

Figure 2(b) shows the thermal degradation of the pristine catheter, the PNVCL homopolymer, and the grafted catheters measured by TGA. The thermograms showed that the pristine silicone presents the highest thermal stability with a 10% weight loss at 507°C and a decomposition temperature at 662°C . In contrast, the PNVCL homopolymer showed the lowest thermal resistance with a loss of 10% by weight at 291°C and a decomposition temperature of 447°C . For their part, the grafting materials SRcat-g-PNVCL(25%) and SRcat-g-PNVCL(35%) presented a weight loss of 10% at temperatures of 442 and 422°C , and two decomposition temperatures at 456 and 626°C for those modified with 25% PNVCL and at 448 and 636°C for the modified ones with 35%. These results show the presence of the two polymers in the grafting materials.

On the other hand, Fig. 2(c) shows the results of the water swelling tests for the grafting materials; the test was carried

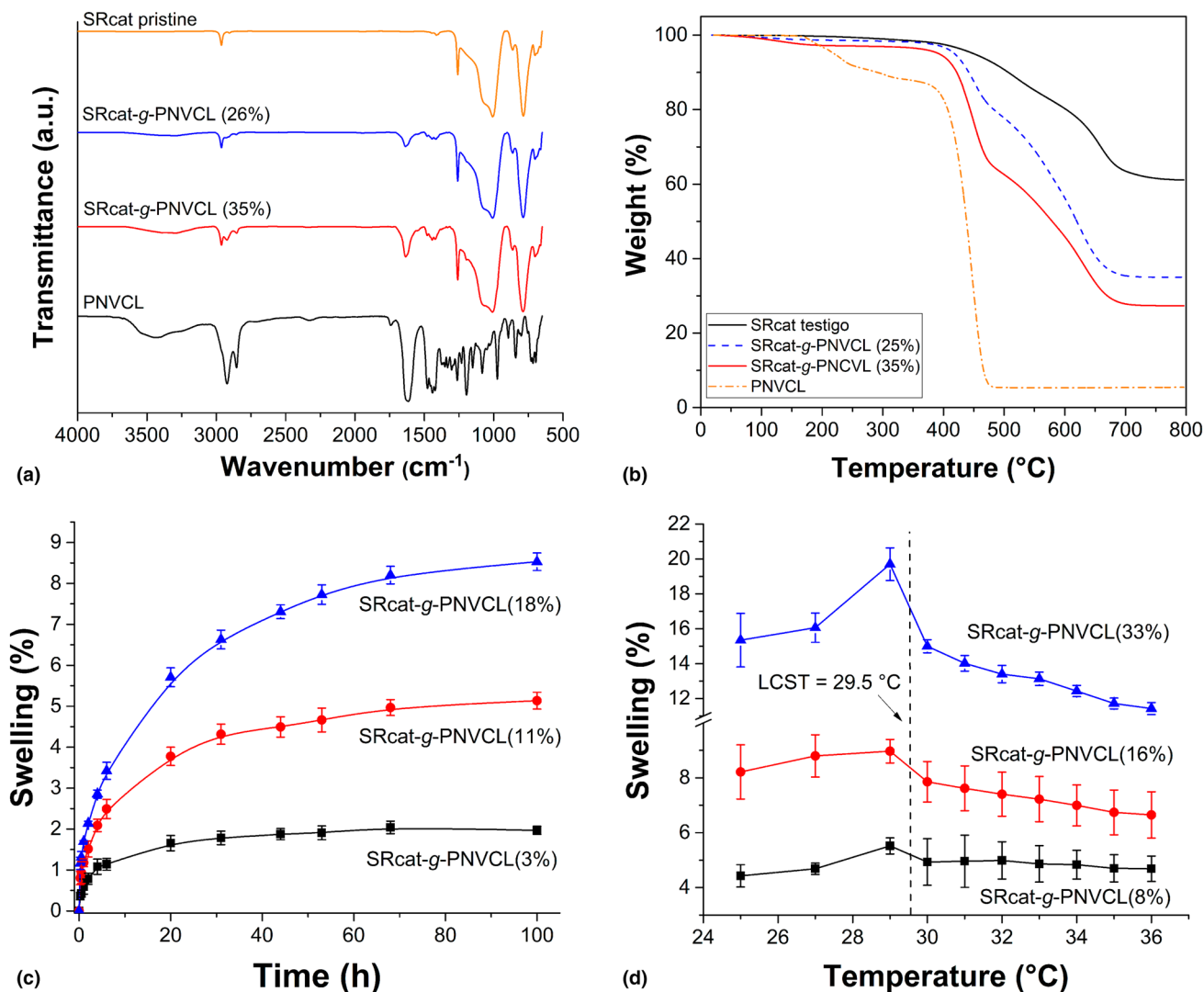


Figure 2. (a) Infrared spectra of the pristine and grafted silicone catheters using ATR, (b) Thermograms of pristine and grafted silicone, (c) Swelling curves in water at 25°C, and (d) Thermo-responsive assays.

out at 25°C. Silicone catheter is a hydrophobic material that does not interact with water, so it does not swell. However, the catheters grafted with PNVCV gained hydrophilicity, which increased with increasing grafting percentage. This behavior was also observed in the contact angle assays where the unmodified silicone catheters had angles of $103 \pm 2^\circ$, while the grafted ones showed angles of $92 \pm 2^\circ$, $100 \pm 1^\circ$, and $93 \pm 2^\circ$ depending on the grafting percentage 3, 11, and 18%.

Finally, Fig. 2(d) shows the swelling in water of the grafted materials when varying the temperature. PNVCV is a thermo-responsive polymer whose homopolymer has an LCST between 32 and 34°C; however, this temperature can be displaced when PNVCV is copolymerized. The grafted silicone catheters with PNVCV, unlike the original catheter, showed thermo-response with an LCST at 29.5°C. This critical temperature is lower than the body temperature, so

the system has the potential for the drug release in response to the stimulus.

Load and release of vancomycin

Vancomycin is an antibiotic used to treat infections caused by gram-positive bacteria, such as *S. aureus*. Vancomycin has functional groups in its structure that allow its interaction with the grafted material. The charge of vancomycin was determined by UV-Vis spectroscopy, it was observed that the materials obtained a maximum charge after 2 h of interaction with the solution of drug managing to load 1.1 ± 0.18 mg/g for SRcat-g-PNVCL (3%), 0.82 ± 0.02 mg/g for SRcat-g-PNVCL (10%), and 0.62 ± 0.09 mg/g for SRcat-g-PNVCL(18%). Figure 3 shows the release profiles of vancomycin from the grafting catheters. The three profiles were fitted to the Peppas-Sahlin model using the software DDsolver of Excel,^[25] describing a

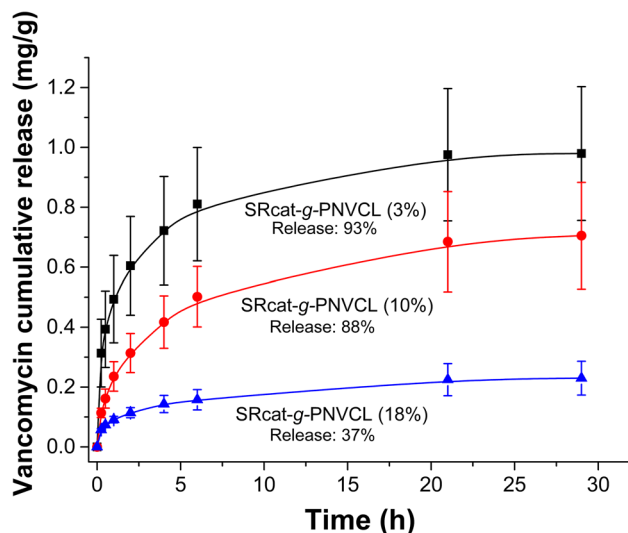


Figure 3. Vancomycin release profiles (condition: PBS a 37°C).

Table I. Peppas–Sahlin model parameters.

Sample	k_1	k_2	n
SRcat-g-PNVCL(3%)	51.1 ± 9.1	-6.5 ± 2.4	0.40 ± 0.09
SRcat-g-PNVCL(10%)	38.8 ± 5.1	-3.7 ± 0.9	0.45 ± 0.01
SRcat-g-PNVCL(18%)	41.6 ± 1.3	-5.8 ± 1.6	0.40 ± 0.09

release system controlled by two ways: drug diffusion and the relationship of the polymer chains.^[26,27] The Eq. 5 shows the mathematical equation of the Peppas-Sahlin model:

$$M_t/M_\infty = k_1 t^n + k_2 t^{2n}, \quad (5)$$

where M_t/M_∞ is the rate between the amount of drug in determined time and the amount of drug in the equilibrium state, k_1 is de Fickian diffusion contribution, k_2 is the polymer chains relaxation contribution, and n is the Fickian diffusion exponent. The release constants of the materials shown in Table 1 indicate that the release is regulated by diffusion.

Although all materials carry a similar amount of vancomycin, the material grafted with 3% PNVCL is the one that allows the highest release, 93%, which was attributed to a lower interaction with the drug that allows the drug release. The amount of drug released decreased with increasing graft percentage, indicating an affinity increase between the drug and the grafted polymer, avoiding the diffusion of the drug.

Conclusions

PNVCL grafting was achieved on silicone catheters using the direct irradiation method, obtaining grafts in the range from 3 to 35%, depending on the conditions. Toluene turned out to be the best solvent for the grafting process, and maximum grafting was achieved with 30% monomer and 50 kGy. All the modified materials presented thermo-sensitivity and the ability to

load and release vancomycin; however, the material with 3% PNVCL graft was the one that showed the highest release with a release percentage of 93%. These results show the antimicrobial potential of the grafted material.

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Author contributions

Conceptualization: MUR-F, LD-P, and EB; Methodology: MUR-F and LD-P; Formal analysis and investigation: LD-P and EB; Writing—original draft preparation: LD-P and EB; Writing—review and editing: LD-P and EB; Funding acquisition: EB; Resources: EB; and Supervision: EB.

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Data availability

No applicable.

Declarations

Competing interest

The authors have no competing interest to declare that are relevant to the content of this article.

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