



BIOPHARMA

Benchtop NMR as a Versatile Tool for Quality Control: Example of Poloxamer Compendial Testing

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Innovation with Integrity

Poloxamers are essential nonionic surfactants in pharmaceutical formulations. Their composition significantly influences their functional properties, necessitating NMR analysis for regulatory compliance as outlined in their USP-NF and Ph. Eur. monographs. The Bruker Fourier 80 benchtop NMR spectrometer is an ideal solution for such testing: it meets all technical requirements of the monographs, while bringing NMR capabilities in a compact, cryogen-free system, well-suited for quality control laboratories. Based on years of experience, Bruker GxP kits support achieving the required full compliance with the regulatory requirements without compromising ease of use and automation features.

Poloxamers are a class of triblock copolymers, consisting of a central polypropylene oxide (PPO) block linked to two polyethylene oxide (PEO) chains (Figure 1). They are archetypical examples of nonionic surfactants, the PPO core being hydrophobic while the PEO chains provide the hydrophilicity. Since their first patent by BASF in the 1950s as detergents, they have garnered significant and growing attention in pharmaceutical formulations.¹ Originally introduced under the trade name Pluronic[®],² these synthetic polymers gained prominence for their ability to stabilize pharmaceutical formulations by reducing surface and interfacial tensions. This is crucial in preventing protein aggregation and denaturation. Among the various marketed products, Poloxamer 188 and Poloxamer 407 have been particularly noted for their efficacy in drug solubilization and stabilization, demonstrating safe and effective use across multiple drug formulations.³

¹ Kabanov et al., *Journal of Controlled Release*, **2002**, 82, 189-21

² Several trade names have since emerged such as Lutrol[®], Kolliphor[®], Antaro[®], and Synperonics[®].

³ Thomas et al. *Acta Biomaterialia*, **2020**, 110, 37-67; Muniz et al. *Biomaterials Advances*, **2023**, 151, 213484

Poloxamers are particularly important in protein-based therapeutics or biologics, which are prone to instability and aggregation. In this context, poloxamers not only enhance the physical stability of these sensitive molecules but also improve their bioavailability and therapeutic efficacy.⁴ Comparatively, poloxamers present advantages over traditional pharmaceutical surfactants like polysorbates, which have been associated with issues such as degradation and particulate formation under stress conditions.⁵ Thus poloxamers are increasingly preferred in formulations that are susceptible to oxidative stress or require stringent storage conditions.³

Pharmacopeias have acknowledged the importance of poloxamers by including them in the excipient/reagent categories for many years. Both the major United States Pharmacopeia-National Formulary (USP-NF) and the European Pharmacopoeia (Ph. Eur.) have a monograph⁶ describing a range of poloxamers, as illustrated in Table 1, while the Chinese Pharmacopeia focuses, for example on the most common poloxamers 188 and 407, with identical specifications. Yet it should be noted that the references listed in these monographs represent only a fraction of the various poloxamers commercially available.

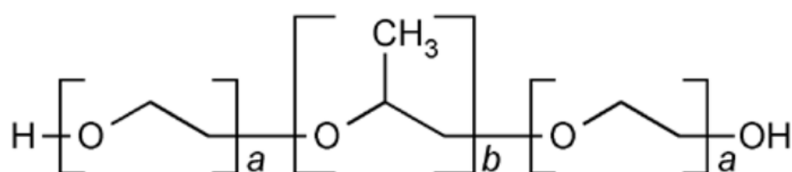


Figure 1 Schematic structure of poloxamer as reported in USP-NF.

Poloxamer	Physical Form	Average Molecular Weight	Weight % Oxyethylene	a	b
124	Liquid	2090 to 2360	46.7 ± 1.9	12	20
188	Solid	7680 to 9510	81.8 ± 1.9	80	27
237	Solid	6840 to 8830	72.4 ± 1.9	64	37
338	Solid	12700 to 17400	83.1 ± 1.7	141	44
407	Solid	9840 to 14600	73.2 ± 1.7	101	56

Table 1 Poloxamer specifications of the USP-NF monograph. Ph. Eur. monograph specifications are identical except for the a and b values indicated as ranges.

Since the self-assembly and thermogelling properties of poloxamers are intrinsically connected to the length and ratio of each block,⁷ control of these characteristics is crucial to ensure the conformity of a given batch of product for pharmaceutical use. This is overall achieved in both the USP-NF and Ph. Eur. monographs by a combination of two methods:⁸

- A dedicated, titration-based methodology to measure the overall average molecular weight.
- A Nuclear Magnetic Resonance (NMR) method to determine the weight percent of oxyethylene (also known as PEO content or EO/PO ratio), which directly correlates to the ratio between the a and b blocks.

⁴ Lamprecht et al. *Pharmaceutics* **2022**, *14*, 2575

⁵ Wang et al. *J. Pharm. Sci.* **2019**, *3*, 1264-1271; Grapentin et al. *J. Pharm. Sci.*, **2020**, *109*, 2393-2404

⁶ Numbered 1464 in Ph. Eur.

⁷ The “xyz” number used in monographs indicate the actual ratio and length. The digits xy multiplied by a factor of 100 corresponds to the approximate molecular mass of the oxypropylene center and z multiplied by 10 describes the oxyethylene content in percentage. Not all trade names however use the same nomenclature.

⁸ Ph. Eur. also uses an additional IR-based method for identification.

NMR spectroscopy is a very well-established method for structural characterization. In the case of polymers, NMR is the only analytical technique able to provide detailed characterization of their composition and probe their microstructure, with the significant advantages of being inherently quantitative and non-destructive. Determining the ratio of repetitive units in block copolymers is thus straightforward with NMR, while practically impossible with any other techniques, or at least without very significant effort such as complete denaturation of the product. Average chain length (and thus average molecular weight in number) can also be generally determined for well-defined polymeric structures, exploiting the chain-end resonances. Modern NMR approaches such as diffusion-ordered spectroscopy (DOSY) can also give direct access to information about the statistical distribution similarly to size exclusion chromatography (SEC).

Pharmacopeia methodologies, however, intend to rely on the most “accessible” procedure in regards of equipment and expertise. For a long time, NMR was perceived as a technique to avoid for compendial procedures due to the cost of the systems and the level of expertise required. Although NMR has been rapidly established as one of the fundamental analytical techniques in academia, its availability in the private sector was much more limited, and GMP-compliant systems were even rarer. This paradigm is now rapidly changing. Spectrometers are simpler to use and can be operated on a routine basis by non-experts, because of significant improvements in user interfaces, fully automated procedures, and simplified maintenance operations. The recent progress in GMP compliance of NMR spectrometers and the introduction of benchtop systems have also further accelerated the process, as evidenced by the recent introduction of NMR in the ICH Q2(R2) and the revised USP <761> and <1761>.⁹

In this historical context, the procedure for the control of the overall average molecular weight in the poloxamer monograph is a typical example: a lengthy and tedious chemical titration methodology was, at the time, chosen over NMR or SEC as it only requires a few chemicals and glassware. If this choice could be revisited nowadays, no alternative was found from the beginning for the weight percent oxyethylene determination, and NMR was indeed introduced as the compendial tool. As such, the historical poloxamer monographs can be seen as a precursor for the introduction of modern techniques in pharmacopeias.

The weight percent oxyethylene testing of poloxamer by NMR is straightforward: it consists of a simple sample preparation (dissolution in a deuterated solvent), spectrum acquisition and data analysis. Details of the analytical procedures described in the USP-NF and the Ph. Eur. are thus very similar. The only significant differences are that the Ph. Eur. only indicates CDCl₃ as the solvent while the USP-NF indicates both D₂O and CDCl₃ as possibilities but requires the presence of a chemical shift standard (DDS or TMS), and more surprisingly requests the addition of one drop of D₂O if CDCl₃ is used. This latter instruction has been probably ignored by many laboratories, but formal justification should be provided in the local standard operating procedure. In both cases, determination of the weight percent oxyethylene is directly accessible using the ratio of integrals from the ¹H NMR spectrum. NMR being an absolute method, the areas of the resonances are indeed directly proportional to the number of associated nuclei and can be leveraged for molar ratio determination. In the present case, the area A₂ (3.8-3.2 ppm) accounts for the two repetitive units of the block copolymer (signal from CH₂/CH of the oxypropylene and oxyethylene units) while the area A₁ (around 1.08 ppm) is specific to the CH₃ group the oxypropylene unit (see Figure 2).¹⁰ The monographs directly provide the formula (reported below) to convert these raw relative integration values into the final weight % oxyethylene results, to be compared with the specification:¹¹

$$\%W_{oxyethylene} = \frac{3300 \alpha}{33 \alpha + 58} \text{ where } \alpha = \frac{A_2}{A_1} - 1$$

Equation 1

⁹ Effective as of December 1st, 2025.

¹⁰ Areas are reported as specified in the monographs.

¹¹ See application note “[Quantification of Oxyethylene in Poloxamers in Full Automation on the Fourier 80](#)” for detailed explanation of the equation.

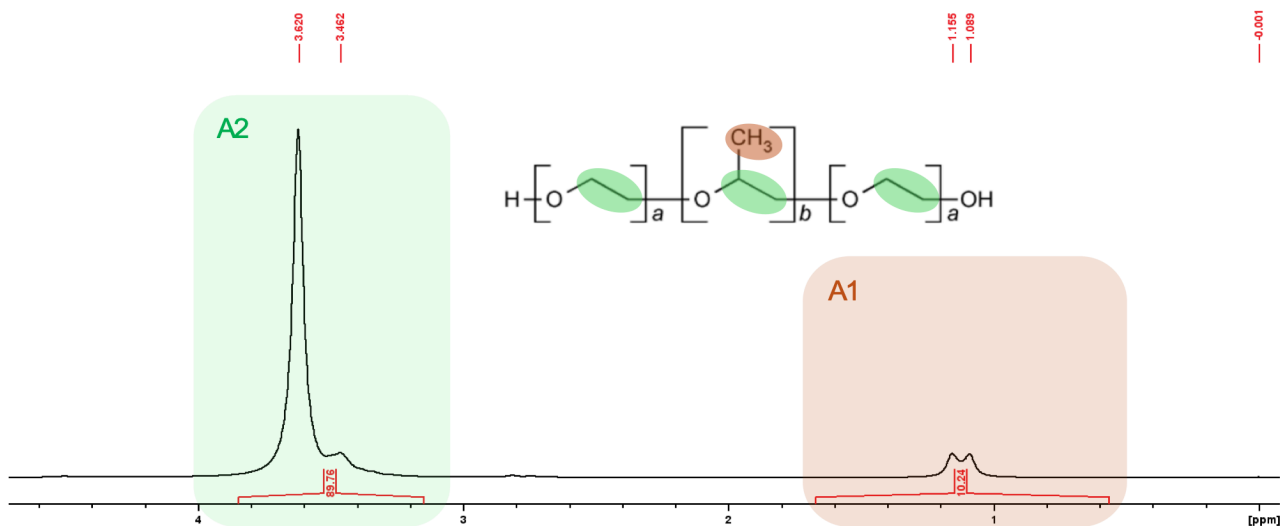


Figure 2: Example of a ^1H spectrum of a typical poloxamer 188 recorded on Fourier 80 according to USP-NF and Ph. Eur. in CDCl_3 . A1 and A2 areas as defined in the monographs are shown in color with their structural attribution.

As demonstrated in the spectra (Figure 2), the two regions of interest, A1 and A2, are distinctly separate and the resolution of a benchtop NMR spectrometer such as the Bruker Fourier 80 significantly exceeds the requirements for individual integration of these areas. Although inherently less sensitive and resolved than high-field NMR spectrometers, the performances of the Fourier 80 spectrometer are optimally suited for such compendial testing. This system largely mitigates the challenges associated with deploying high-field NMR spectrometers in quality control laboratories while providing the simplicity and robustness required for routine testing. Table 2 and Figure 3 demonstrate the Fourier 80 successful application in verifying the conformity of various commercial poloxamers (tested according to the USP-NF and Ph. Eur. monographs in CDCl_3), including two specified in Table 1.

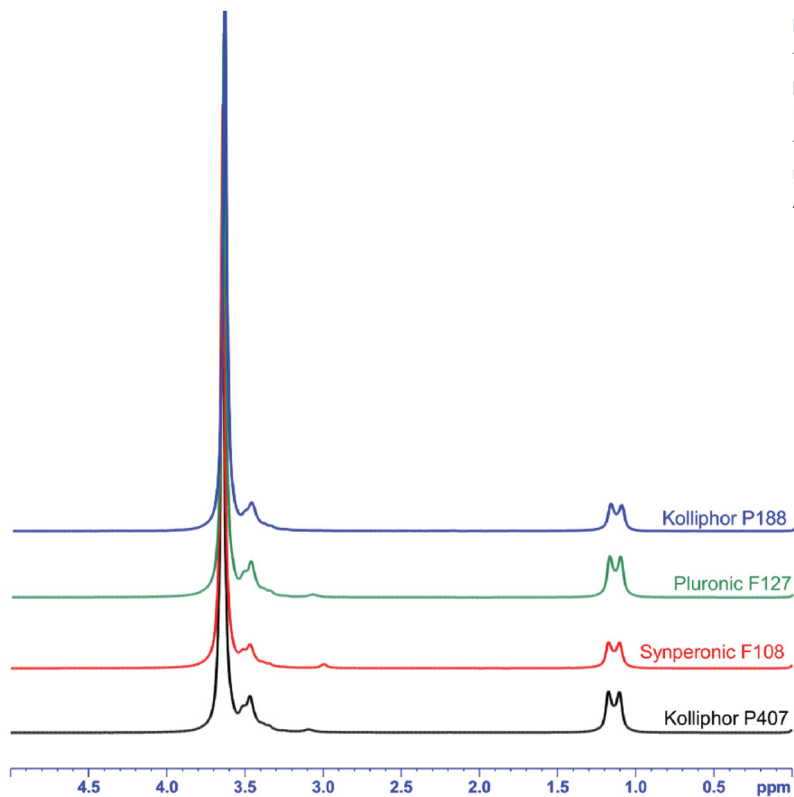


Figure 3 ^1H NMR spectra of four commercially available poloxamers recorded on Fourier 80 according to the USP-NF and Ph. Eur. monographs (zoom on the A1 and A2 regions).

Poloxamer	POE Number	Determined POE Content (%w/w)	Published POE Content (%w/w)
Kolliphor® P188	P188	80.4	80.3
Kolliphor® P407	P407	72.7	72.5
Synperonic® F108	P308	80.2	approx. 80
Pluronic® F127	P367	72.6	approx. 70

Table 2: Examples of PEO content testing using the Fourier 80 according to USP-NF and Ph. Eur. on commercial poloxamers.

To further underscore the precision of the NMR method even at lower fields, Table 3 presents the results of a repeatability study conducted on eight individual preparations of a poloxamer 188 batch. This study yielded a remarkable standard deviation of 0.2%, which is well within the most stringent USP-NF precision criteria of not more than 1% (applicable to drug substances, not excipients).

Sample	Determined POE Content (%w/w)
#1	80.1
#2	80.4
#3	80.6
#4	80.3
#5	80.5
#6	80.4
#7	80.3
#8	80.6
Average	80.4
%RSD	0.2%

Table 3: Results of a precision study for POE content testing using the Fourier 80 according to USP-NF and Ph. Eur. monographs (8 individual preparations of a poloxamer 188 batch).

Moreover, as an additional testament to the general robustness of NMR methods, retained with the Fourier 80, the determination of the weight percentage of oxyethylene was also performed at significantly lower concentrations, with dilutions of up to a factor of 60 (equivalent to 1 mg in 0.6 mL of CDCl₃). These concentrations were substantially below the minimum concentration stipulated by the monographs, yet the determined values (Table 4) remained within acceptable limits, only marginally exceeding the 3 σ interval based on the aforementioned repeatability results. While operating near the limit of quantification is not relevant for pure product testing, this scenario exemplifies the large operable range afforded by NMR-based analytical procedures.

Kolliphor® P188	Determined POE Content (%w/w)	SNR
4 mg	80.3	47.89
2 mg	80.1	27.55
1 mg	79.8	11.83

Table 4: Example of the impact of dilution for POE content testing using the Fourier 80 according to USP-NF and Ph. Eur. SNR is the signal to noise of the signal in the A1 region determined using a 2 ppm noise area.

Finally, robustness in routine testing also requires automation to eliminate operator induced variability. To this end, the Advanced Chemical Profiling 2.0 (ACP) software now enables fully automated, sample to report workflows. It integrates directly with the Fourier 80 main software (TopSpin, IconNMR and GoScan), allowing non expert users to execute virtually any NMR based procedure while ensuring that the method remains fit for purpose. For routine analyses, ACP opera-

tes in the background, with no user intervention beyond selecting the desired analytical method during sample submission. All subsequent steps are carried out under full automation, culminating in a report in which quantitative results are expressed according to the relevant monographs and/or standard operating procedures, without the need for additional data interpretation or calculation steps (Figure 4).

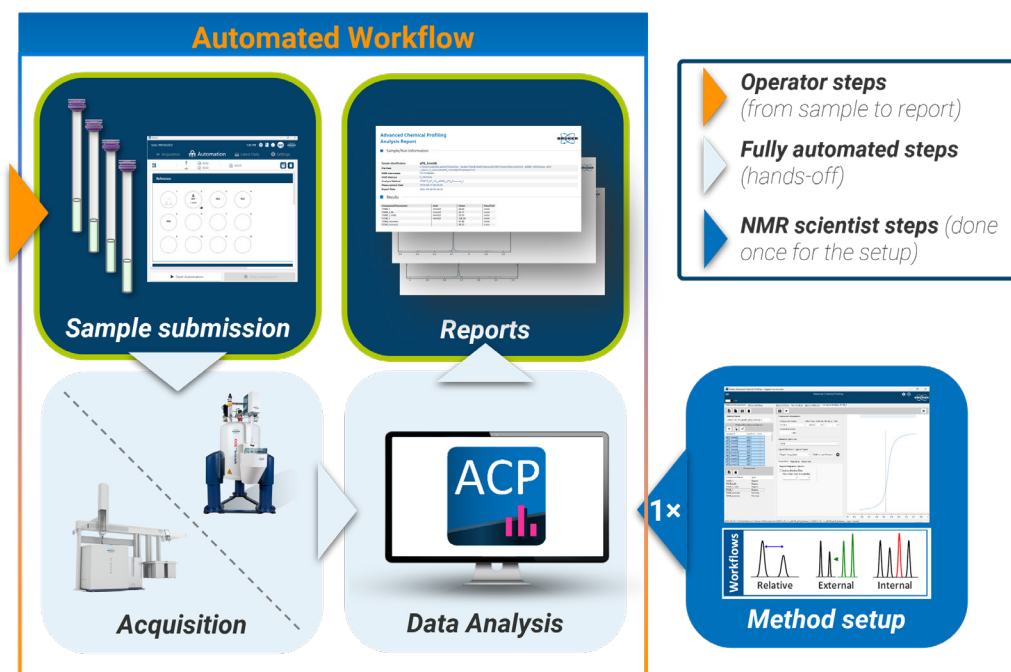


Figure 4 Schematic workflow enabled by ACP. Once set up, an NMR method can be performed under full automation by routine users. Following sample submission, all acquisition, processing and analysis steps are performed in the background and end up with the generation of a report containing the reportable values.

A detailed discussion of ACP capabilities, workflows and examples for polymeric raw material testing is available in a separate document.¹² NMR testing of poloxamers is a particularly clear illustration of the benefits of ACP, as the monograph procedure can be implemented in just a few steps for routine use. Data acquisition, processing and analysis are then performed automatically, directly delivering to the user a human and/or machine readable report containing the weight percent oxyethylene result as defined in the compendia. When configured, an optional pass/fail statement is added to support immediate interpretation (Figure 5).

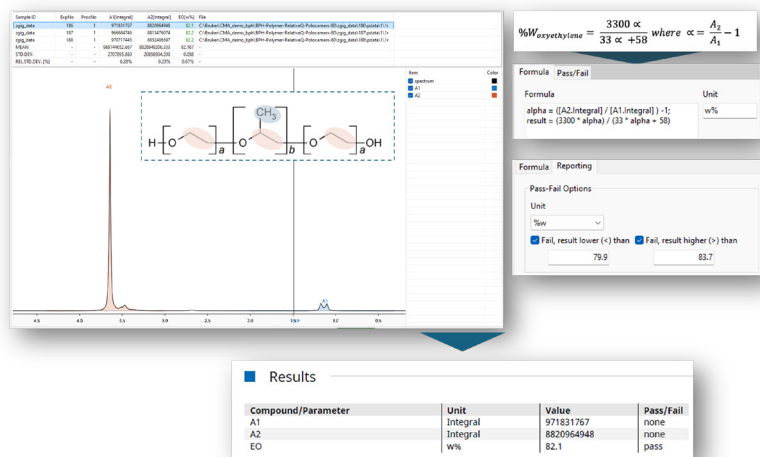


Figure 5 Example of the setup of an automated analysis of poloxamer 188 according to USP-NF and Ph. Eur. 1464 using the Fourier 80 and ACP. The two sets of resonances that need to be integrated and the reportable value (%w oxyethylene) are defined in the ACP method. As a result, they can be directly reported as part of fully automated analytical process, including the delivery of pass/fail conclusions according to the monograph acceptance criteria.

¹² See [Enabling Scalable and Reproducible NMR Analysis for Polymeric Raw Materials in Pharma QC](#), November 2025

Leveraging the latest advancements in hardware and software technology, the benchtop Fourier 80 NMR spectrometer thus presents an ideal solution for performing the compendial analyses exemplified herein. This system is well suited for QC laboratories, offering a compact, cryogen free setup that requires minimal maintenance while still providing the benefits and performances associated with an NMR spectrometer within a laboratory environment. Based on one of the most versatile and robust analytical techniques available, this system can be utilized for a broad range of NMR based compendial tests or bespoke qualitative and quantitative procedures.¹³ Additionally, it serves as a powerful tool for investigating out of specification and out of trend results originating from other analytical methods, enabling rapid examination of mixtures or identification of unknown products.

As a concluding note, it must be emphasized that, as with all compendial procedures, execution of the weight percent oxyethylene test must adhere strictly to pharmaceutical regulations. This encompasses not only the systematic implementation of the monograph requirements but also those of the associated general chapters of the relevant pharmacopeia and, more broadly, the local regulations governing pharmaceutical testing, such as cGMP. While these general frameworks are well established within testing laboratories, the nuances associated with NMR are often less familiar. In the case of the poloxamer monographs, both USP–NF and Ph. Eur. provide limited descriptions of the NMR method, necessitating consultation of the corresponding NMR general chapters¹⁴ to ensure that the procedure is suitable for its intended purpose. This process also involves defining the protocol and criteria for procedure verification prior to routine use.¹⁵ For non expert users, the technical considerations contained within these general chapters may appear daunting. This potential barrier can now be alleviated by ACP, which enables analysts to perform routine NMR testing without requiring specialized expertise. Combined with the Bruker GxP Readiness Kits for the Fourier 80, it allows laboratories to benefit from NMR in regulated environments without requiring specialized expertise for routine operations.

¹³ Several other examples are available at [Benchtop NMR for Quality Control](#)

¹⁴ <761> for USP-NF, 2.2.33 for Ph. Eur.

¹⁵ As required by USP-NF <1226>

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