December 2020

Ultrapure 100 Handbook

For purification of plasmid DNA using the Ultrapure 100 Buffer Set and QIAGEN® anion-exchange resin

Sample to Insight

QIAGEN

Contents

Kit Contents

Ultrapure 100 Buffer Set	
Catalog no.	**11910**
Buffer P1	4 x 500 ml
Buffer P2	4 x 500 ml
Buffer P3	4 x 500 ml
Buffer QBT	500 ml
Buffer QC	6 x 500 ml
Buffer QN	510 ml
Endotoxin-Free Water	17 ml
Buffer TE	240 ml
Buffer ER	500 ml
RNAse A	4 x 50 mg
Quick-Start Protocol	1

Storage

The Ultrapure 100 Buffer Set should be stored dry at room temperature (15–25°C). The buffers can be stored under these conditions for up to 2 years without showing any reduction in performance and quality. After adding RNase A, Buffer P1 should be stored at 2–8°C and is stable for 6 months.

Intended Use

The Ultrapure 100 Buffer Set is intended for molecular biology applications. This product is not intended for the diagnosis, prevention, or treatment of a disease.

All due care and attention should be exercised in the handling of the products. We recommend all users of QIAGEN products to adhere to the NIH guidelines that have been developed for recombinant DNA experiments or to other applicable guidelines.

Safety Information

When working with chemicals, always wear a suitable lab coat, disposable gloves, and protective goggles. For more information, please consult the appropriate safety data sheets (SDSs). These are available online in convenient and compact PDF format at **www.qiagen.com/safety**, where you can find, view, and print the SDS for each QIAGEN kit and kit component.

Quality Control

In accordance with QIAGEN's ISO-certified Quality Management System, each lot of Ultrapure 100 Buffer Set is tested against predetermined specifications to ensure consistent product quality.

Introduction

The Ultrapure System allows endotoxin-free (<0.1 EU/µg DNA) plasmid DNA to be easily and efficiently purified. The system is based on the remarkable selectivity of patented QIAGEN resin with integrated endotoxin removal to yield ultrapure DNA. The exceptional separation properties result in DNA purity equivalent or superior to that obtained by 2 successive rounds of CsCl gradient centrifugation. Purified DNA is suitable for sensitive applications, including plasmid DNA-mediated gene silencing, transfection, and gene therapy research.

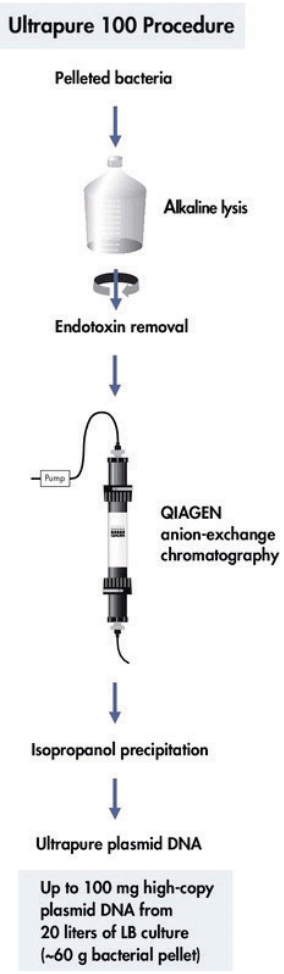
Principle

The level of endotoxin contamination in purified plasmid DNA depends on the purification method used. Silica-slurry–purified DNA exhibits extremely high endotoxin levels. QIAGEN, QIAfilter, HiSpeed® Plasmid Kits, and 2x CsCl ultracentrifugation yield very pure DNA with relatively low levels of endotoxin. The QIAGEN Ultrapure System includes an integrated endotoxin-removal step to yield plasmid DNA containing <0.1 EU/µg plasmid DNA.

Endotoxins, also known as lipopolysaccharides or LPS, are cell membrane components of Gram-negative bacteria such as *Escherichia coli*. Endotoxins are released during the lysis step of plasmid DNA purification and significantly reduce transfection efficiencies in endotoxin sensitive cell lines. Furthermore, endotoxins can influence the uptake of plasmid DNA in transfection experiments by competing with DNA for "free" transfection reagent. Endotoxins also induce nonspecific activation of immune responses in immune cells such as macrophages and B cells, which can lead to misinterpretation of transfection results. These responses include induced synthesis of proteins and lipids such as IL-1 and prostaglandin. Overall, endotoxins represent a noncontrollable variable in transfection experiment setup, influencing the outcome and reproducibility of results and making them difficult to compare and interpret. In gene therapy research, endotoxins can interfere by causing endotoxic shock syndrome and activation of the complement cascade.

Principle and procedure

The bacterial biomass is lysed under alkaline conditions, and the lysate is cleared by centrifugation (see the flowchart below). Endotoxins are removed using the special endotoxin removal buffer, and the lysate is loaded onto the QIAGEN anion-exchange resin for DNA purification.



Equipment and Reagents to Be Supplied by User

When working with chemicals, always wear a suitable lab coat, disposable gloves, and protective goggles. For more information, consult the appropriate safety data sheets (SDSs), available from the product supplier.

- Centrifuge
- Filters; we recommend Grade 597 ½ Qualitative Filter Papers or Grade 595 ½ Qualitative Filter Papers (cat. nos. 10311847 or 10311651, respectively) from Whatman (see **https://www.cytivalifesciences.com/en/us/solutions/lab-filtration**)*
- Isopropanol
- Ethanol, 70%
- Ultrapure 100 Buffer Set or buffers prepared according to the Appendix, page 20
- Ultrapure Resin 500 (cat. no. 11500)
- Vantage L Laboratory Column VL 44 x 250 (cat. no. 96440250) from Merck (**www.merckmillipore.com**) filled with 135 g QIAGEN Ultrapure Resin 500

* This is not a complete list of suppliers and does not include many alternative vendors of biological supplies.

Important Notes

Plasmid DNA copy number and expected plasmid DNA yield

We recommend the use of only high-copy plasmid DNA with this system. The expected yield for a high-copy plasmid DNA is 3–5 mg from 1 liter of a properly prepared Luria Bertani (LB) culture incubated on a shaker. Low-copy plasmid DNA are not recommended for use with the Ultrapure System. If the use of low-copy plasmid DNA cannot be avoided, protocol modifications may be required and yield may be significantly reduced. Contact QIAGEN Technical Services or your local distributor (see back cover or visit **www.qiagen.com**) for recommendations.

Optimal plasmid DNA yields are dependent upon proper growth conditions. Temperature, shaker speed, culture vessel dimensions, bacterial strain, and antibiotic concentration must be carefully considered. On average, a healthy 1 liter culture yields a pellet with a wet weight of approximately 3–4 g. Never use a pellet with a wet weight of >60 g.

We recommend the use of LB media. Enriched media may be used to reduce the required culture volume; however, growth dynamics will be considerably different and must be adjusted accordingly. The maximum pellet wet weight to be loaded onto the column is 60 g, regardless of the growth media used.

To estimate the total amount of plasmid DNA expected from the Ultrapure preparation, we highly recommend performing a test miniprep using 3.0–5.0 ml of the original culture with a QIAGEN-tip 20 from the QIAGEN Plasmid Mini Kit (cat. nos. 12123 and 12125). The performance of the Ultrapure 100 Buffer Set is not guaranteed when parameters other than those provided in the protocol are used.

Column usage

The QIAGEN anion-exchange resin is for single use only. Ensure that the maximum pressure within the column does not exceed 7 kg/cm^2 (100 psi) to protect the column from damage. The performance of the resin is not guaranteed when parameters other than those given in the protocol are used.

Endotoxin-free DNA

For the preparation of endotoxin-free DNA, use the endotoxin-free buffers provided with the Ultrapure 100 Buffer Set. If glass tubes or pipets are used for any step after elution, ensure that these are heated to 180°C overnight to destroy any endotoxins. Alternatively, use pyrogen-free disposable plasticware.

Protocol: Purification of Plasmid DNA using the Ultrapure 100 Buffer Set

This protocol is for purification of up to 100 mg plasmid DNA from 20 liters of bacterial culture (corresponding to a pellet with a wet weight of approx. 60 g).

Important points before starting

- Add RNase A to Buffer P1 to a final concentration of 100 µg/ml. Ensure that the RNase A is completely dissolved in Buffer P1.
- Prechill Buffer P3 to 4°C.
- Equipment and buffers except Buffer P3 should be equilibrated to room temperature (15–25°C).
- For endotoxin-free DNA, prepare endotoxin-free 70% ethanol just before use by adding 96–100% ethanol to the endotoxin-free water supplied with the Ultrapure 100 Buffer Set.
- When not using the Ultrapure 100 Buffer Set, buffers should be prepared as described in the Appendix, page 20.

Table 1. Buffer volumes required for plasmid DNA preparation from different volumes of overnight LB culture*

Recommended column	Culture volume	Pellet wet weight	Buffer			
			P1, P2, P3	QBT	QC	QF, QN
QIAGEN-tip 2500	500 ml	1650 mg	50 ml	35 ml	200 ml	35 ml
QIAGEN-tip 10000	2500 ml	8250 mg	125 ml	75 ml	600 ml	75 ml
Vantage L Laboratory Column VL 44 x 250	10 liters	30 g	0.5 liter	350 ml	3.0 liters	400 ml
Vantage L Laboratory Column VL 44 x 250	20 liters	60 g	1.0 liter	350 ml	3.0 liters	400 ml

* Expected plasmid DNA yields are 3–5 µg/ml LB for high-copy plasmid DNA (e.g., pBluescript®, pUC, pTZ, and pGEM®) and 0.1–2 µg/ml LB for low-copy (e.g., pBR322 and cosmids).

Procedure

1. Resuspend the bacterial pellet in 1000 ml Buffer P1 containing RNase A.

   Optimal resuspension of the bacterial pellet can be achieved in a 5 liter flask using a submerged stirring paddle set at a low speed to avoid shearing of genomic DNA and generation of foam. The pellet should be completely resuspended after 1–1.5 h.

2. Add 1000 ml Buffer P2, mix by gently inverting the bottle 5–6 times, and incubate at room temperature (15–25°C) for 5 min.

   During lysis, the mixture becomes very viscous. Do not allow lysis to proceed for longer than 5 min.

3. Add 1000 ml of chilled Buffer P3, mix by inverting the bottle 5–6 times, and incubate on ice for at least 30 min.

   After addition of Buffer P3, the solution becomes cloudy.

4. Centrifuge at 4°C for at least 30 min at 11,300–17,700 x *g*. Transfer the supernatant promptly to a fresh vessel.

   Centrifugation should be performed in 500 ml polypropylene centrifugation bottles (e.g., Nalgene, cat. no. 3141-0500). To avoid leakage, do not fill the bottles with more than 450 ml lysate. After centrifugation, the supernatant should be clear.

5. Filter the supernatant through a premoistened, folded filter.

   During this step, incubate the cleared lysate on ice.

6. Optional: To prepare endotoxin-free plasmid DNA, add 1/10 volume of Buffer ER (included in the Ultrapure 100 Buffer Set) to the cleared lysate and incubate for 1 h on ice (see also step 8).

   After the addition of Buffer ER, the lysate appears turbid but will become clear again during incubation on ice.

7. Equilibrate the column with 350 ml Buffer QBT at a flow rate of 10–20 ml/min.

   During this step, incubate the cleared lysate on ice.

   Connect the inlet tube of the column (see the flowchart on page 7) to the silicon tube of the peristaltic pump. The inlet tube is used for loading the cleared lysate and buffers. Make sure that all fittings are secure, for example, by using cable binders to prevent leakage.

8. Load the cleared lysate from step 5 or 6 onto the column at a flow rate of 4–25 ml/min.

   Confirm the flow rate by directly measuring the flow of buffer through the column. A 3000 ml lysate may be loaded in 2–12 h depending on the flow rate chosen. It is often convenient to load the column overnight. Cool the cleared lysate bottle during the entire duration of the column loading either in a refrigerator at 4°C or in an ice bath. Do not cool the column.

9. Wash the column with 3.0 liters of Buffer QC at a flow rate of 20–30 ml/min.

10. Elute the plasmid DNA with 400 ml Buffer QN at a flow rate of 10 ml/min.

11. Precipitate the DNA with 0.7 volumes of room-temperature isopropanol and centrifuge at 4°C at 20,000 x *g* for 30 min or at 10,000 x *g* for 60 min.

    Isopropanol precipitation of the DNA with solutions is equilibrated to room temperature (15–25°C) to minimize salt precipitation. Centrifugation is carried out at 4°C to prevent overheating of the sample and should be performed in 250 ml or 500 ml polypropylene centrifuge bottles or several 50 ml tubes (Nalgene, cat. nos. 3141-0250, 3141-0500, and 3119-0050, respectively).

12. Carefully remove the supernatant, wash the DNA with 20 ml room-temperature 70% ethanol, and centrifuge at ≥15,000 x *g* for 20 min at 4°C. For the preparation of endotoxin-free DNA, use freshly prepared, endotoxin-free, 70% ethanol.

    Ethanol, 70% solution, removes any precipitated salt and replaces isopropanol with ethanol, which is more volatile, yielding DNA that is easier to resuspend.

13. Remove ethanol completely, air-dry for approximately 20 min, and redissolve in a suitable volume of buffer. To obtain DNA free of endotoxins, use the endotoxin-free Buffer TE supplied with the Ultrapure 100 Buffer Set.

    Overdrying the pellet will make the DNA very difficult to redissolve. Resuspend the DNA pellet by rinsing the walls of the tube to recover the DNA, especially when glass tubes are used. The appropriate volume of resuspension buffer can be determined based on the results of the pilot minipreparation (see page 10). Avoid pipetting the DNA up and down to promote resuspension as it may cause shearing.

Troubleshooting Guide

This troubleshooting guide may be helpful in solving any problems that may arise. For more information, see also the Frequently Asked Questions page at our Technical Support Center: **www.qiagen.com/FAQ/FAQList.aspx**. The scientists in QIAGEN Technical Services are always happy to answer any questions you may have about either the information and protocols in this handbook or sample and assay technologies (for contact information, visit **support.qiagen.com**).

	Comments and suggestions
Statement of the problem	
No DNA in lysate	
a) The plasmid DNA did not propagate	Please read "Growth of Bacterial Cultures" on our Web page **www.qiagen.com/dna-references**, and check if the conditions for optimal growth were met.
b) Alkaline lysis was inefficient	If cells have grown to very high densities or if a larger amount of cultured medium than recommended was used, the ratio of biomass to lysis reagent is shifted. This may result in poor lysis conditions because the volumes of Buffers P1, P2, and P3 are not sufficient for setting the plasmid DNA free efficiently. Reduce the culture volume or increase the volumes of Buffers P1, P2, and P3. Also, insufficient mixing of lysis reagents will result in reduced yield. Mix thoroughly after addition of Buffers P1, P2, and P3 to achieve homogeneous suspensions.
c) Insufficient lysis for low-copy plasmid DNA	For low-copy plasmid DNA preparations, doubling the volumes of lysis buffers P1, P2, and P3 may help to increase the plasmid DNA yield and quality (see background information on our Web page: **www.qiagen.com/growth-of-bacterial-culture**).
d) Lysate incorrectly prepared	Check Buffer P2 for SDS precipitation resulting from low storage temperatures and dissolve the SDS by warming. The bottle containing Buffer P2 should always be closed immediately after use. Lysis buffers prepared in the laboratory should be prepared according to the instructions on page 20. If necessary, prepare fresh Buffers P1, P2, and P3.

		Comments and suggestions
The DNA in the flow-through fraction		
a)	Column was overloaded	Check the culture volume and yield against the capacity of the column, as detailed at the beginning of the protocol. Reduce the culture volume accordingly. For very low-copy-number plasmid DNA and cosmid preps requiring very large culture volumes, please see **www.qiagen.com/dna-workingwithdna**.
b)	SDS (or other ionic detergent) was in lysate	Chill Buffer P3 before use. If the lysate is cleared by centrifugation, load onto the column promptly after centrifugation. If the lysate is too viscous for effective mixing of Buffer P3, reduce culture volume or increase volumes of Buffers P1, P2, and P3.
c)	Inappropriate salt or pH conditions in buffers	Ensure that any buffers prepared in the laboratory were prepared according to the instructions provided on page 20.
The DNA in Buffer QC wash fraction		
a)	The column was overloaded	Check the culture volume and yield against the capacity of the resin, as detailed at the beginning of the protocol. Reduce the culture volume accordingly. For very low-copy-number plasmid DNA and cosmid preps requiring very large culture volumes, please see **www.qiagen.com/dna-workingwithdna**.
b)	Buffer QC was incorrect	Check pH and salt concentration of Buffer QC. Recover the DNA by precipitation, and purify on a new QIAGEN-tip.
No DNA in eluate		
a)	No DNA in the lysate	See section "No DNA in lysate" page 15.
b)	Elution Buffer QN was incorrect	Check pH and salt concentration of Buffer QN. Recover the DNA by eluting with fresh buffer.
c)	The DNA passed through in the flow-through or wash fraction	See the previous two sections.

		Comments and suggestions
Little or no DNA after precipitation		
a)	The DNA failed to precipitate	Ensure that the precipitate is centrifuged at ≥15,000 x *g* for 30 min. Recover the DNA by centrifuging for longer and at higher speeds. Try another isopropanol batch.
b)	The DNA pellet was lost	Isopropanol pellets are glassy and may be difficult to see. Mark the outside of the tube before centrifugation. Isopropanol pellets may also be loosely attached to the side of the tube, so pour supernatant off gently.
c)	The DNA was poorly redissolved	Check if the DNA is completely redissolved. Be sure to wash any DNA off the walls, particularly if glass tubes and a fixed-angle rotor are used. Up to half of the total DNA may be smeared on the walls. Alternatively, a swinging bucket rotor can be used to ensure that the pellet is located at the bottom of the tube.
The plasmid DNA difficult to redissolve		
a)	Pellet was overdried	Air-dry pellet instead of using a vacuum, especially if the DNA is of high molecular weight. Redissolve the DNA by warming the solution slightly and allowing more time for redissolving.
b)	Residual isopropanol in pellet	Ensure that pellets are washed with 70% ethanol to remove traces of isopropanol. Redissolve the DNA by warming the solution slightly and allowing more time for redissolving. Increase volume of buffer used for redissolving if necessary.
c)	Too much salt in pellet	Ensure that isopropanol is at room temperature (15–25°C) for precipitation and wash the pellet twice with room-temperature 70% ethanol. Recover the DNA by increasing the volume of buffer used for redissolving.
d)	Buffer pH was too low	Ensure that the pH of the buffer used for redissolving is ≥8.0, since the DNA does not dissolve well in acidic solutions.
e)	Resuspension volume too low	Increase resuspension volume if the solution above the pellet is highly viscous.

		Comments and suggestions
Contaminated DNA/poor-quality DNA		
a)	Genomic DNA in the eluate	Mixing of bacterial lysate was too vigorous. The lysate should not be vortexed after addition of Buffers P2 and P3 to prevent shearing of chromosomal DNA. Reduce culture volume if lysate is too viscous for gentle mixing.
b)	RNA in the eluate	RNase A digestion was insufficient. Check culture volume against recommended volumes and reduce if necessary. Check that the RNase A provided with the kit has been used. If Buffer P1 is more than 6 months old, add more RNase A. Recover the DNA by precipitating the eluate, digesting with RNase A, and purifying on a new QIAGEN-tip.
c)	Nuclease contamination	Check buffers for nuclease contamination and replace if necessary. Use new glassware and plasticware, and wear gloves.
d)	Lysis time was too long	Ensure that the lysis step (Buffer P2) does not exceed 5 min.
e)	Overloaded alkaline lysis	Check the culture volume and yield against the capacity of the column. Reduce the culture volume accordingly or alternatively increase the volumes of Buffers P1, P2, and P3.
f)	The plasmid DNA is nicked/sheared/degraded	The DNA was poorly buffered. Redissolve the DNA in Buffer TE, pH 8.0, to inhibit nuclease activity and maintain stable pH during storage.
g)	Shearing during redissolving	Redissolve the DNA gently, without vortexing or vigorous pipetting. Avoid using small pipet tips.
h)	Particles in redissolved the DNA	Centrifuge the DNA solution and transfer supernatant to a new tube. The particles have no effect on DNA quality.
Poor DNA performance		
a)	Too much salt in pellet	Ensure that isopropanol is at room temperature (15–25°C) for precipitation and wash the pellet twice with room-temperature 70% ethanol. Precipitate the DNA again to remove the salt.
b)	Residual protein	Check culture volume against the recommended volumes and reduce if necessary. Ensure that the bacterial lysate is cleared properly by centrifugation Check *g*-force and centrifugation time.

	Comments and suggestions
Extra DNA bands on analytical gel	
a) Dimer form of plasmid DNA	Dimers or multimers of supercoiled plasmid DNA are formed during replication of plasmid DNA. Typically, when the purified plasmid DNA is electrophoresed, both the supercoiled monomer and dimer form of the plasmid DNA are detected upon ethidium bromide staining of the gel. The ratio of these forms is often host dependent.
b) The plasmid DNA has formed denatured supercoils	This species runs faster than closed circular DNA on a gel and is resistant to restriction digestion. Do not incubate cells for longer than 5 min in Buffer P2. Mix immediately after addition of Buffer P3.
Blocked column	
Lysate was turbid	Ensure that the lysate is clear before it is loaded onto the column. Ensure that Buffer P3 is chilled before use. Check *g*-force and centrifugation time.
Endotoxin content higher than expected	
a) Incubation time with Buffer ER too short	Ensure that the lysate is incubated on ice for 30 min for efficient endotoxin removal. Immediately after addition of Buffer ER, the lysate appears turbid but becomes clear again during ice incubation. The clearing of the lysate indicates sufficient incubation time.
b) Recontamination of the DNA after preparation	Use only plasticware and glassware that is certified to be pyrogen- or endotoxin-free. Never autoclave plasticware or glassware in autoclaves that have previously been used for bacteria. Use only water that is certified to be endotoxin-free for the preparation of 70% ethanol. Resuspend the DNA in endotoxin-free Buffer TE.
Lysate becomes turbid during the binding step on the column	
	This is due to the temperature change from ice incubation to the binding step at room temperature (15–25°C), and this has no negative effect on the performance of QIAGEN resin.

Appendix: Buffer Preparation

Table 2. Buffer compositions required for plasmid DNA preparation

Buffer	Buffer composition
Buffer P1 (resuspension)	50 mM Tris·HCl, pH 8.0; 10 mM EDTA; 100 µg/ml RNase A
Buffer P2 (lysis)	200 mM NaOH, 1% SDS
Buffer P3 (neutralization)	3.0 M KAc, pH 5.5
Buffer QBT (equilibration)	750 mM NaCl; 50 mM MOPS, pH 7.0; 15% isopropanol; 0.15% Triton® X-100
Buffer QC (wash)	1.0 M NaCl; 50 mM MOPS, pH 7.0; 15% isopropanol
Buffer QN (elution)	1.6 M NaCl; 50 mM MOPS, pH 7.0; 15% isopropanol

For a supplementary protocol describing how to recycle and fill the chromatography column with QIAGEN anion-exchange resin (as powder or slurry), visit **www.qiagen.com/ultrapure100bufferset**.

Ordering Information

Product	Contents	Cat. no.
Ultrapure 100 Buffer Set	Buffers P1, P2, P3, QBT, QC, QN, ER, TE, Endotoxin-free water, and RNase A; for preparation of up to 100 mg plasmid DNA	11910
Ultrapure Resin 500	A total of 675 g QIAGEN anion-exchange resin, sufficient for 5 refills	11500

For up-to-date licensing information and product-specific disclaimers, see the respective QIAGEN kit handbook or user manual. QIAGEN kit handbooks and user manuals are available at **www.qiagen.com** or can be requested from QIAGEN Technical Services or your local distributor.

Document Revision History

Date	Changes
12/2020	Corrected the typographical error of the value of RNase A from 4 x 50 µg to 4 x 50 mg. Updated the details in section “Equipment and Reagents to Be Supplied by User”. Updated the URLs in section “Troubleshooting Guide” and Appendix.

Notes

Limited License Agreement for Ultrapure 100 Buffer Set

Use of this product signifies the agreement of any purchaser or user of the product to the following terms:

1. The product may be used solely in accordance with the protocols provided with the product and this handbook and for use with components contained in the kit only. QIAGEN grants no license under any of its intellectual property to use or incorporate the enclosed components of this kit with any components not included within this kit except as described in the protocols provided with the product, this handbook, and additional protocols available at www.qiagen.com. Some of these additional protocols have been provided by QIAGEN users for QIAGEN users. These protocols have not been thoroughly tested or optimized by QIAGEN. QIAGEN neither guarantees them nor warrants that they do not infringe the rights of third-parties.
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