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BACHELOR'S THESIS

Chemical engineering degree

PFS SILICONE OIL PARTICLES IN PLACEBO SOLUTIONS & DEVICE COMPARATION

Report and Annexes

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Resum

Les xeringues precarregades permeten el subministrament de fàrmacs injectables en un format senzill per al seu posterior ús i asseguren que el pacient rebi el dosatge adequat. Tot i així, aquest format de subministrament té també certs desavantatges com és la presència de l'oli de silicona. Aquest serveix per a lubricar i suavitzar la pressió necessària per treure el contingut de la xeringa però per contrapartida, es pot alliberar en forma de partícules subvisibles a la solució.

Per tal d'avaluar el nombre de partícules subvisibles disperses en una solució existeixen diversos mètodes basats en principis diferents. En aquest estudi s'utilitzen dos mètodes – un basat en el principi de l'enfosquiment de llum i l'altre basat en la comparació microscòpica d'imatges de membrana – els quals es comparen entre sí, així com, s'estudia l'estabilitat en les mesures de cada un dels aparells per separat. D'aquest estudi s'obté resultats que es poden considerar estadísticament iguals amb un 95% de confiança.

Un cop definida l'estabilitat de les mesures i una primera hipòtesi sobre la relació dels resultats d'ambdós aparells, s'estudia l'evolució del nombre de partícules subvisibles que es troben en 5 dissolucions placebo emmagatzemades en xeringues precarregades. Per aquest estudi es defineixen com a variables el temps (de 0 fins a 5 setmanes) i la temperatura (5 °C i 25 °C) en la que s'emmagatzemen les mostres i també s'estudien els resultats després de sotmetre-les a 24 h d'agitació a 300 rpm.

Les mostres de les xeringues precarregades s'analitzen amb els dos mètodes prèviament comparats. D'aquesta forma es pot verificar en quins casos es compleix la hipòtesi definida prèviament i en quins no, així com, l'evolució del nombre de partícules al llarg del temps de l'estudi. Els resultats posen de manifest que per a les mostres emmagatzemades a 5 °C la tendència és a mantenir el nombre de partícules constant, mentre que en les altres condicions no s'ha pogut definir una tendència general.

Resumen

Las jeringuillas precargadas permiten el subministro de fármacos inyectables en un formato sencillo para su uso posterior y aseguran que el paciente reciba la dosis adecuada. Sin embargo, este formato de subministro tiene ciertas desventajas como la presencia de aceite de silicona. Este sirve para lubricar i suavizar la presión necesaria para extraer el contenido de la jeringuilla pero por contrapartida, se puede liberar en forma de partículas subvisibles en la solución.

Para evaluar el número de partículas subvisibles dispersas en una solución existen diversos métodos basados en distintos principios. En este estudio se utilizan dos métodos – uno basado en el oscurecimiento de la luz y el otro basado en la comparación microscópica de imágenes de membrana – los cuales se comparan entre sí, así como se estudia la estabilidad de cada uno de los instrumentos utilizados independientemente. De este estudio se obtiene que los resultados de los dos se pueden considerar estadísticamente iguales con un nivel de confianza del 95%.

Una vez definida la estabilidad de las medidas y la primera hipótesis sobre la relación de resultados de los dos instrumentos comparados, se estudia la evolución del número de partículas que se encuentran en 5 disoluciones placebo almacenadas en jeringuillas precargadas. Para este estudio de definen como variables el tiempo (de 0 a 5 semanas) i la temperatura (5°C y 25°C) en que se almacenan las jeringuillas y también se estudian los efectos de someterlas a 24 h de agitación a 300 rpm.

Las muestras de las jeringuillas precargadas se analizan con los dos métodos comparados anteriormente. De este modo se verifica en que casos se cumple la hipótesis definida previamente y en cuales no, así como, también se estudia la evolución de partículas detectadas a lo largo del estudio. Finalmente, se obtiene que para las muestras almacenadas a 5 °C la tendencia es a mantener constante el número de partículas mientras que en las otras condiciones estudiadas no se define ninguna tendencia general.

Abstract

Pre-filled syringes allow for the sub-delivery of injectable drugs in a simple format for later use and ensure that the patient receives the appropriate dose. However, there are disadvantages to this delivery format, such as the presence of silicone oil. This serves to lubricate and soften the pressure needed to draw the contents of the syringe, but on the other hand, it can be released as subvisible particles in the solution.

To assess the number of subvisible particles dispersed in a solution, there are several methods based on different principles. In this study, two methods are used - one based on light obscuration and the other based on backgrounded membrane imaging - which are compared with each other, as well as the stability of each of the instruments used independently. From this study, the results of both devices can be considered statistically equal with a confidence level of 95%.

Once the stability of the measurements and the first hypothesis on the relationship between the results of both devices compared have been defined, the evolution of the subvisible particles count found in 5 placebo solutions stored in pre-filled syringes is studied. For this study, the time (0 to 5 weeks) and the temperature (5°C and 25°C) at which the syringes are stored are defined as variables, and it is also studied the effect of subjecting them to 24 h of mechanical stress (agitation at 300 rpm).

Samples of the pre-filled syringes are analysed with the two methods compared above. In this way, it is verified in which cases the previously defined hypothesis is fulfilled and in which it is not, as well as the evolution of particles detected throughout the study. Finally, it is obtained that for the samples stored at 5 °C the tendency is to keep the number of particles constant, while in the other conditions studied no general tendency is defined.

Glossary

Word/ Abbreviation	Description
BMI	Abbreviation for Backgrounded Membrane Imaging.
Compendial technique	Technique described in the Pharmacopeia or that has been approved for being regulatory in some area.
IPA	Abbreviation for Isopropanol.
LF	Abbreviation for Laminar flow.
LO	Abbreviation for Light obscuration.
P188	Abbreviation for Poloxamer 188.
Parenteral	Introduced to the body though a different route than the digestive channel, usually used to refer to injections.
PFS	Abbreviation for Pre-filled syringes.
Placebo	Substance without pharmacological effect.
PS20	Abbreviation for Polysorbate 20.
Vial	Small glass container to hold liquids or drugs.

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1 Introduction

1.1 Purposes

This study has two main purposes. The first of them is to determine if the silicone oil found in pre- filled syringes interacts with the solution inside generating an increment in the number of subvisible particles detected – in this study, 5 different placebo solutions are studied –. In the study, different storage conditions (temperature, time, agitation) are evaluated. Thereby, it is expected to be able to determine if any of this these variables have some relevant impact on the results.

The other purpose of the study is to do an instrument evaluation. The subvisible particle count is measured using 2 different analytical methods based on different principles. The first part of the instrumental evaluation consists of a variability study of each of the instruments used. The second part of this instrument evaluation is a comparison between both devices used. For this device comparison, the study has the aim to determine if it exists some differences between the results obtained with HIAC device (subvisible particle count based on Light obscuration) and with HORIZON VUE device (subvisible particle count based on Backgrounded Membrane Imaging) when measuring the same solution. In addition to that, in case this study shows that it's a difference between the results of both devices, this study also would have the purpose to develop a preliminary model that can describe and quantify this difference.

1.2 Scope of the study

The present study has been developed in the *Research and Process Development* department of Sanofi-Aventis Deutschland GmbH (Frankfurt am Main, Germany). The materials and analytics used in the study have been agreed to develop a study that can cover the interest of the present report but also provide information of interest to the hosting company.

Part of the learning gained in the development of this project is the method used throughout. The experimental part has been developed using the working method of the receiving company, which together with the knowledge obtained during the bachelor made it possible to carry out the complete study.

This study can be divided into 2 main parts, one referring to the device variability and comparison study and the other one referring to the study of the PFS silicone oil effect. Even though the analytical plan has been designed to obtain some results statistically significant, due to the limited time and resources, the results can't provide a final conclusive statement. However, they can be understood as a significant first approach.

2 Theoretical framework

2.1 Pre-filled syringes (PFS)

Because of the progress of new technologies, the world of medicine and drugs is constantly expanding, developing new therapies, and trying to optimize drug production and supply. The research tries to obtain an easy and safe way to administrate the drug to the final user, especially when this administration is done by non-expert people themselves out from a health center. This administration process, and its complexity, are very different when talking from different administration routes.

Among all the medicament administration routes, the parenteral route is used when immediate action is required, and the drug can't be delivered through other existing routes, such as oral, inhaled, or rectal routes among others.

Parenteral drug administration is understood as the route relating to inject the drug directly into the body. Conventionally, injectable drugs were always supplied in vials or ampoules and the syringe had to be filled at the same moment as injecting the drug into the patient. In the mid-20th century, the injectable drug supply perspective changed because of the development of pre-filled syringes. This ready-to-use syringes provide safety and efficacy advantages at the same time they can ensure that the final user is receiving properly the dosage, established by the manufacturer.

These advantages of the PFS above the vials and ampoules made this drug delivery system for injectable drugs gain acceptance in the market. With the increase of acceptance of the method, the use of PFS increased giving rise to numerous types of PFSs available in the market nowadays. Nonetheless, all the different types of PFS have 3 main parts: the needle, the barrel, and the plunger. The different types of pre-filled can be classified into 2 types depending on the needle configuration. The *Staked needle PFS* has the characteristic that the needle type and gauge are chosen by the manufacturer, and it can't be separated from the barrel. On the other side, the *Luer lock tip PFS* doesn't incorporate the needle by itself. In this case, the needle must be locked to the barrel via a Luer lock with a screw cap mechanism

In the next figure is shown an example picture of the parts of a *Staked needle PFS* and a *Luer lock tip PFS*.

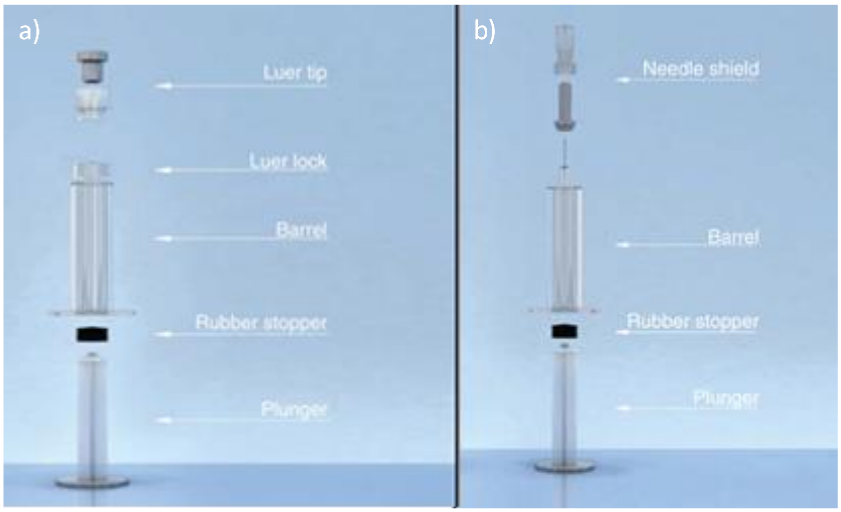

Figure 2.1: a) Luer lock tip PFS parts; b) Staked needle PFS parts [11]

One of the biggest inconveniences of PFS is that, because of the PFS design (plunger-barrel), the syringe barrel must be recovered with silicone oil to lubricate and ensure to easily deliver the content inside. The storage of protein-based drugs in these barrels with silicone can sometimes cause silicone leaching into the product. When storing a protein-based drug, the PFS rubber stoppers can also release some contaminant particles that could end in the drug. The different PFS manufacturers are studying a way to reduce these adverse effects and, even now is used a specialized silicone that reduces the likeliness of silicon leaching, it is still a not solved problem that presents this drug delivery system

2.2 Subvisible particle count methods

2.2.1 Light obscuration (LO)

Light obscuration (LO) is the compendial technique for the analysis of subvisible particles in injections and parentals. For the measurements with this analytical technique, the sample is introduced into the device through a thin needle. The sample flow passes through a laser beam and the particles found in it block a certain amount of light. This light block produces a "shadow" on a light-sensitive detector that is analysed by the detector and the equivalent circular diameter of the particle is obtained. To be able to obtain the equivalent circular diameter from the "shadow" produced, the device must be calibrated based on polystyrene particles of a known size.

Advantages and disadvantages of light obscuration

The main advantages of LO are:

- High sampling efficiency: all the sample volume can be analysed during the measurement.
- Short time needed to perform the measurement.
- Short time needed to obtain the results.
- Recognized by the Pharmacopeia.

The main disadvantages of LO are:

- Bubbles in solutions detected as particles; the bubbles change the light direction and are detected as particles increasing the real particle count.
- The sample ends up in waste after the analysis.
- Turbulent samples and samples with a high viscosity can't be measured with this method.
- Require washing some of the components between measurements.

2.2.2 Backgrounded Membrane imaging (BMI)

Backgrounded Membrane Imaging is an analytical technique that has its roots in membrane microscopy. In this initial technique, the samples were filtered, and the particles found in the samples were retained in the filter used. After that filtration process, the particles captured in the filter were manually counted using a microscope, a process that can be tedious and require a lot of time.

BMI can be understood as an automatization of membrane microscopy. Using image-processing a single device can analyse images and acquire the particle data of the sample. The process starts with a background image of the membrane. After that, the sample is placed in the membrane and filtered retaining the particles in the membrane. Once the filtration is done, the membrane is re-imaged. Using sophisticated image-processing techniques, the sample image is precisely aligned with the background

first obtained. Then, both images are subtracted on a pixel-by-pixel basis eliminating the background of the sample image and revealing the BMI image where the particles are shown.

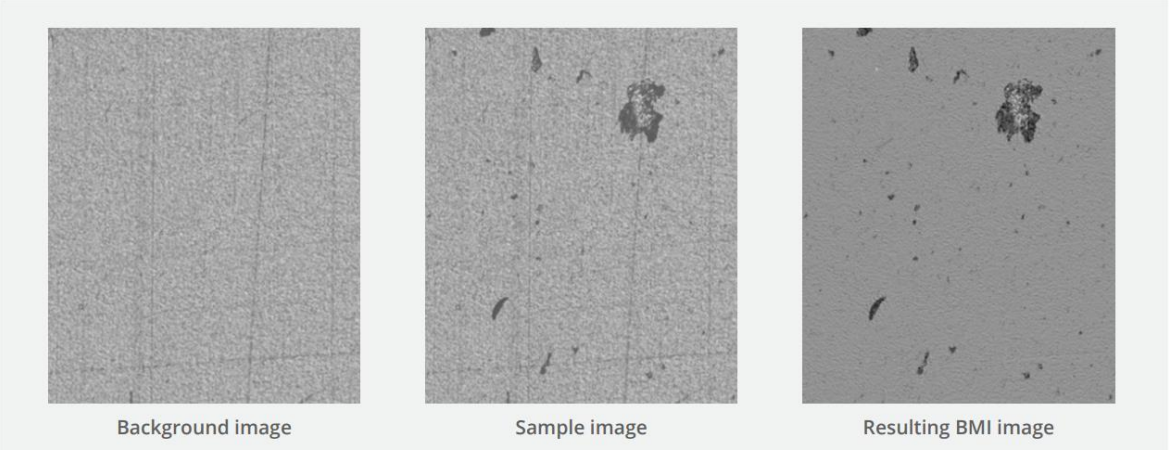

Figure 2.2: BMI image-processing [2]

Advantages and disadvantages of backgrounded membrane imaging

The main advantages of BMI are:

- Is needed a short volume of the sample to perform the analysis (25 µL).
- The air bubbles don't affect the results; they are eliminated during the filtration.
- Particles are retained in the membrane and can be analysed later with other instruments.
- Provides images of the particles; can help to determine the origin or to detect some sample contamination.
- No need of washing any component.

The main disadvantages of BMI are:

- Require more time and material to perform the measurement.
- Not recognised for the quality control by the Pharmacopeia.

3 Materials & method

3.1 Analytical plan

The analytical plan followed in this study can be divided into 2 big parts. The first one can be understood as a preliminary study focused on device evaluation and comparison. With the results obtained in this first part, is done the device variability study, and is developed the first approach to the comparison between both devices used (HORIZON VUE and HIAC).

The second part of the analytical plan consists of the study of the PFS itself. From this second part of analytics are obtained the results needed to evaluate the effect of PFS silicone oil effect on the placebo solutions inside. In addition, the results obtained in this second part verify the approach done in the first part of the study (preliminary study).

3.1.1 Preliminary study analytical plan

For this first part of the study, is pretended to have enough number of samples comparable to each other so, all the tests must analyse the same formulation. Nevertheless, for being able to consider the external conditions in the device variability study the tests are divided into 3 consecutive days. The composition of the formulation used for this part of the study is summarized in the next table.

Table 3.1: Preliminary study formulation

Component	Concentration
Acetate	10 mM
Poloxamer 188 (P188)	4000 ppm
Sucrose	8 % (w/v)

The analysis included in this part of the study is the measurement of subvisible particles with HIAC and with HORIZON VUE. Initially, it was decided to perform 60 measurements are done with HORIZON VUE (20 each day during 3 consecutive days) and 30 measurements are done with HIAC (10 each day during 3 consecutive days). It must be considered that each of the measurements obtained with HIAC is an average of 3 runs done by the device.

3.1.2 Study in PFS analytical plan

For this part of the study, the main purpose is to obtain results to evaluate the evolution of the solutions inside the pre-filled syringes. To consider the option that different solutions interact in a different way with the silicone oil, 5 formulations are studied. Their characteristics (composition and concentration) of them are summarized in the table below.

Table 3.2: Study in PFS formulations

Formulation	pH	Buffer	Surfactant	Extra excipients
1	7	Phosphate 10 mM	PS20 100ppm	L-Arginine HCl 230mM
2	7	Phosphate 10 mM	P188 200 ppm	L-Arginine HCl 230mM
3	5	Acetate 10 mM	PS20 100ppm	8% Sucrose
4	5	Acetate 10 mM	P188 4000 ppm	8% Sucrose
5	5	Acetate 10 mM	P188 200 ppm	8% Sucrose

During this part of the study, it is planned to analyse the samples at time zero, after 24 hours of agitation and after 1, 2, 3, 4 and 5 weeks stored at 5°C and at 25°C. This makes a total of 12 time points of analysis for each of the 5 formulations.

In each of those points of analysis, the sample will pass 5 analytic processes. These analytics and its feature are summarized in table 6.

Table 3.3: Study in PFS analytics

Feature	Analytics
Picture	Visual assessment
pH	pH
Osmolarity	Osmolarity
Subvisible particles	HIAC (LO)
Subvisible particles	HORIZON VUE (BMI)

3.2 Material

The main material and chemicals used and for the studies are compiled in the next two tables, each one referent to each part of the study. In addition to these materials, it has also been used for the sample preparation a balance, volumetric flasks, beakers), spatulas, pipettes (1 mL, 5 mL, and 20 mL) and a pH-meter. For the sample analysis, it is also used the adequate device for each of the analytics in the study.

Table 3.4: Used Materials for the preliminary study

Component	Manufacturer	Product No.	Lot
Acetic acid	Merk	1.00063.1000	KS0160963814
Sodium acetate trihydrate	Sigma Aldrich	1.28205.1001	0001136143
Poloxamer 188	Merk	1.37112.1000	K53063312110
Sucrose	Pfanstiehl	S-124-2-MC	41676A
Milli-Q water	Merk	MPGP002A1	F1CB62788
12 mL syringe	Omnifix ®	4617207V	-

Table 3.5: Used Materials for the study in PFS

Component	Manufacturer	Product No.	Lot
Acetic acid	Merk	1.00063.1000	KS0160963814
Sodium acetate trihydrate	Sigma Aldrich	1.28205.1001	0001136143

Sodium dihydrogen phosphate monohydrate	Merk	1.06346.0500	AM1456946948
di-Sodium hydrogen phosphate heptahydrate	Sigma Aldrich	1.06574.1000	AM1688174105
Polysorbate 20	Sigma Aldrich	8.17072.1000	K53172372111
Poloxamer 188	Merk	1.37112.1000	K53063312110
L-Arginine HCl	Sigma Aldrich	1.01544.100	K53613844151
Sucrose	Pfanstiehl	S-124-2-MC	41676A
Milli-Q water	Merk	MPGP002A1	F1CB62788
20 mL syringe	Omnifix ®	4617207V	20M23C8
Syringe filter PES: 0,22µm	Sartorius stedim biotech	16532-K	90717103
InVitro Biotainer, PC, Lab pack	Fisher Scientific	3030-42	1320360
Pre-filled syringes (PFS)	Neopak	8200671	6008
Pre-filled syringes (PFS)	Neopak	8200671	6010
SCF stoppers	BD Hypak SCF	47284410	8024652

3.3 Sample preparation

The first step for the sample preparation is the formulation manufacturing. For that is needed to calculate the amount of the different chemicals that must be added to obtain the desired final concentrations at the desired pH.

To obtain the acetate buffer is used acetic acid and sodium acetate trihydrate and for the phosphate buffer is used sodium acetate trihydrate and sodium dihydrogen phosphate monohydrate. To determine the amount of each of the components that must be added to obtain the desired pH (5 and 7 respectively) and concentration are used the 2 equations below.

$$pH = pKa + log\frac{[A^-]}{[HA]} \quad \textbf{Equation 1}$$

$$desired\ concentration = [HA] + [A^-] \quad \textbf{Equation 2}$$

In the case of phosphate buffer, [A-] is the concentration of sodium dihydrogen phosphate monohydrate and [HA] the concentration of di-sodium hydrogen phosphate heptahydrate. In the case of Acetatebuffer, [A-] is the concentration of acetic acid and [HA] the concentration of sodium acetate trihydrate.

For the PS20 and the P188, the amount needed can be calculated as is shown in equation "3".

$$component\ (g) = desired\ volume\ (mL) * desired\ concentration\ (ppm)/10^6 \quad \textbf{Equation 3}$$

The mass of L-arginine HCl and sucrose needed for each formulation can be obtained using equations "4" and "5" respectively.

$$Sucrose\ (g) = desured\ volume\ (mL) * \%(w/v) \quad \textbf{Equation 4}$$

$$L - Arg\ HCl\ (g) = MW_{L-Arg\ HCl} * desired\ concentration\ (M) * desired\ volume(L) \quad \textbf{Equation 5}$$

3.3.1 Preliminary study samples

For this part of the study, only one formulation is needed. To manufacture that formulation, the amount of each component needed is calculated and added to a 50 mL baker. There is added free-particle water until 80-90% of the final volume (40-45 mL) and the pH is adjusted by adding HCl / NaOH. Then the solution is taken to the desired final volume and the final pH is measured and verified that it doesn't have a deviation larger than 0,1 from the desired pH (pH = 5±0,1).
The results of these calculations are shown in the table below.

Table 3.6: Amounts needed and final amounts

Compound	Target amount	Actual amount
Acetic acid	0,01097 g	0,01132 g
Sodium acetate trihydrate	0,04334 g	0,04381 g
P188	0,2000 g	0,20063 g
Sucrose	4,0000 g	4,00109 g

After the manufacturing process, the obtained solution is filtered with a 0,22 µm pore diameter filter and stored in a sterile and particle free recipient. The samples are stored at 5°C until they must be analyzed.

3.3.2 Study in PFS samples

To manufacture the 5 formulations needed for this part of the study in a more efficient way, first some up-concentrated solutions were prepared. These up-concentrated solutions are summarized in "table 7".

Table 3.7: Up-concentrated solutions

Solution	Concentration	Volume
Phosphate buffer	50 mM	50 mL
Acetate buffer	40 mM	100 mL
PS20	100000 ppm	1 mL
P188	20000 ppm	25 mL

To manufacture these up-concentrated solutions, the amount needed of each component is calculated using equations "1", "2", "3" and added to a flask where the solution is taken to the desired volume.

Table 3.8: Up-concentrated solutions amounts

Solution	Compound	Target amount	Actual amount
Phosphate buffer	Sodium dihydrogen phosphate monohydrate	0,21152 g	0,21158 g
Phosphate buffer	di-Sodium hydrogen phosphate heptahydrate	0,25924 g	0,25984 g
Acetate buffer	Acetic acid	0,08773 g	0,08761 g
Acetate buffer	Sodium acetate trihydrate	0,34550 g	0,34542 g
PS20	PS20	0,10000 g	0,10086 g
P188	P188	2,00000 g	2,01190 g

To manufacture the final formulations required for the study, some calculated volumes of the up-concentrated solutions are added to a baker where are mixed with the calculated amount of the extra excipient (L-arginine HCl or sucrose). There is added free-particle water until 80-90% of the final volume (40-45 mL) and the pH is adjusted by adding HCl / NaOH. Then the solution is taken to the desired final volume and the final pH is measured and verified that it doesn't have a deviation larger than 0,1 from the desired pH (pH = 5±0,1 for acetate base buffer and pH = 7±0,1 for phosphate base buffer).

The volume of the up-concentrated solutions needed for each formulation can be calculated as shown in equation "6". The results of these calculations are summarized in "table 5".

$$volume\ needed\ (mL) = \frac{desired\ total\ volume\ (mL) * desired\ concemtration}{up-concentrated\ concentration}$$ **Equation 6**

Table 3.9: Calculated amount to manufacture the formulations

Compound	Target amount	Actual amount
	F1	
Phosphate up-concentrated	20 mL	20 mL
PS 20	0.1 mL	0.1 mL
L-Arginine HCL	4.84541 g	4.84536 g
NaOH	Add to pH 7	pH = 7.033
	F2	
Phosphate up-concentrated	20 mL	20 mL
P188	1 mL	1 mL
L-Arginine HCL	4.84541 g	4.84540 g
NaOH	Add to pH 7	pH = 7.033
	F3	
Acetate up-concentrated	25 mL	25 mL
PS20	0.1 mL	0.1 mL
Sucrose	8.00000 g	8.00614 g
NaOH	Add to pH 5	pH = 5.009
	F4	
Acetate up-concentrated	25 mL	25 mL
PS188	20 mL	1 mL
Sucrose	8.00000 g	8.00477 g
NaOH	Add to pH 5	pH = 5.046
	F5	
Acetate up-concentrated	25 mL	25 mL
P188	1 mL	1 mL
Sucrose	8.00000 g	8.00415 g
NaOH	Add to pH 5	pH = 5.021

After the manufacturing process, each of the manufactured formulations is filtered using a 0,22µm pore diameter filter and the filtrated buffer is stored in a sterilized and particle free recipient. Once the buffers are filtered are stored at 5°C until they are used to fill the pre-filled syringes (PFS).

In this study are used 360 PFS of 1 mL – 72 PFS for each formulation –distributed in the 12 time points of analysis correspond to 6 PFS of 1mL for each formulation at each time point. To fill the syringes, 1mL of the corresponding formulation is set in each PFS through the bottom of the syringe and then, the PFS are closed one by one with adequate stoppers.

After filling and closing all the syringes they are stored under the defined conditions to be able to follow the analytical plan established.

The time zero samples are acquired just after filling the PFS. For the 24 hours of agitation samples, the syringes are stored one day at 5°C and then agitated for 24 hours at 25 °C and 300 rpm (from Thursday 03.03.2022 at 12:53 to Friday 04.03.2022 at 12:55). The other PFS are stored under established conditions until they must be acquired.

3.4 Acquirement of samples

For the first part of the study – Preliminary study – the samples can be analysed directly from the vials where they have been stored for one, two, or three days.

For the second part of the study – study in PFS – the sample acquirement consists of the process of pulling out the formulations from the syringes. At each of the established time points, the content of 6syringes of each formulation is removed from the PFS and added to a vial where it can be analysed. With this process is expected to stop any possible interaction with the silicone oil found in the syringe barrel or the syringe stopper.

It must be taken into consideration that due to a mistake, the samples at time zero were placed in a sterile tube but were not particle free. This can make increase the particle count of these samples and it mustbe noticed for the discussion of the results.

3.5 Analytics techniques

For the visual assessment, the samples are observed in the PFS. With this visual test is analysed if the colour or the opacity of the sample has changed as well as if there have appeared some visible particles in it or if it has occurred some other change in their physical characteristics. To document this test, images of the sample in the PFS are taken with white and black backgrounds. If it is noticed some change, it must be noted and shown in the picture taken.

As the pH measurement and the osmolarity measurements, together with the visual assessment, are used to check the sample. These tests are done twice for each formulation and although 2 measurements of the pH and 2 of the osmolarity for each formulation can't provide results statistically acceptable, they are enough to check the sample. For the pH measurement, is used a pH-meter with

an adequate electrode. For measuring the osmolarity is used the Osmomat 010 that crystalizes a small amount of the sample to obtain the result.

For the subvisible particles determination based on light obscuration is used the HIAC device. It must be properly cleaned with particle free water before running each test. When the results of a test with particle free water are lower that the allowed limit the sample can be analysed. After each measurement, it also must be properly cleaned. Each test with this device uses 0,9 mL of the sample and each test consist of 4 runs where the sample is analysed.

Subvisible particles are also determined using HORIZON VUE, a device that bases its measurement on Backgrounded Membrane Imaging (BMI). For this test, the sample is filtered in a 96 wells plate, and the device compares photos of the filter (well) before and after the filtration process. For each well that is going to be used, the first that should be done is to acquire the background (photo before the filtration). After that, for the filtration process is placed 50 µL of the sample is in each well and filtered using a vacuum pump. After that 100µL of particle free water is placed in each of the used wells to eliminate the resting buffer and it is filtered again using the vacuum pump. Finally, it is dried and set again to the HORIZON VUE to obtain the results.

3.6 Safety measures

When working in a laboratory, there are exists some implicit risks. Therefore, all general safety rules must be followed during the whole experimental procedure. These safety rules consist of wearing lab coat, safety goggles, gloves, closed shoes, and long trousers whenever working in the laboratory.

This study is focused on subvisible particles, which makes the study very noticeable to small external contamination. To prevent external contamination, all the processes done from the formulation filtration must be done inside a laminar flow cabinet. To make sure the inside area of the LF cabinet doesn't contain leftovers from previous experiments, it must be cleaned with a hard surface disinfectant solution containing 70% v/v isopropanol (IPA) before each use

4 Results

4.1 Preliminary study

4.1.1 HORIZON VUE

The next figures are the representation of the results of the sample evaluation with HORIZON VUE. The numerical results obtained are summarized in *"Annex A1. Preliminary study results".*

It must be noticed that due to a procedural accident on the second day, some of the volumes that must be analyzed with HORIZON VUE, were wasted. Because of that, it was only possible to run 10 tests with HORIZON VUE instead of the 20 planned. Nevertheless, this doesn't have a big impact on the study because it was possible to obtain a significant number of tests in all the time points studied.

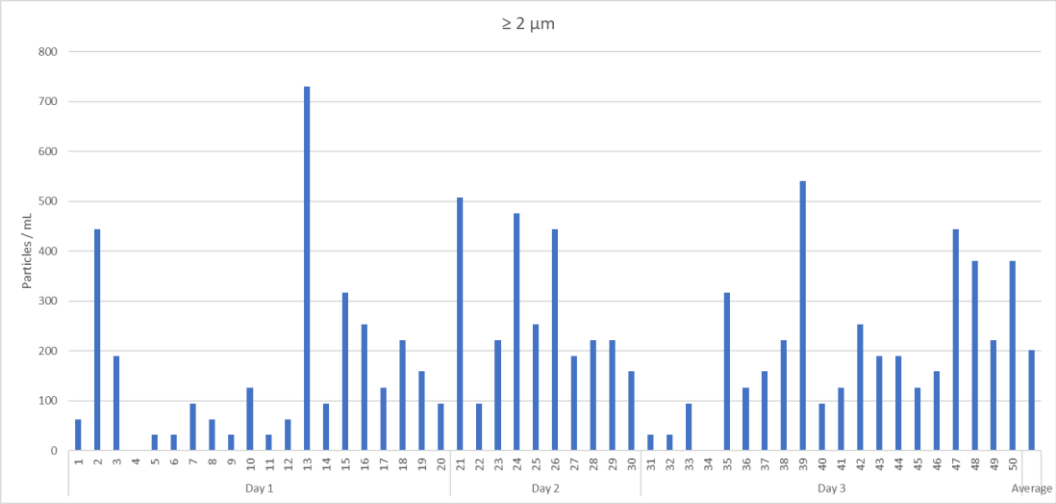

Figure 4.1: HORIZON VUE results for particles with an equivalent diameter ≥ 2 µm

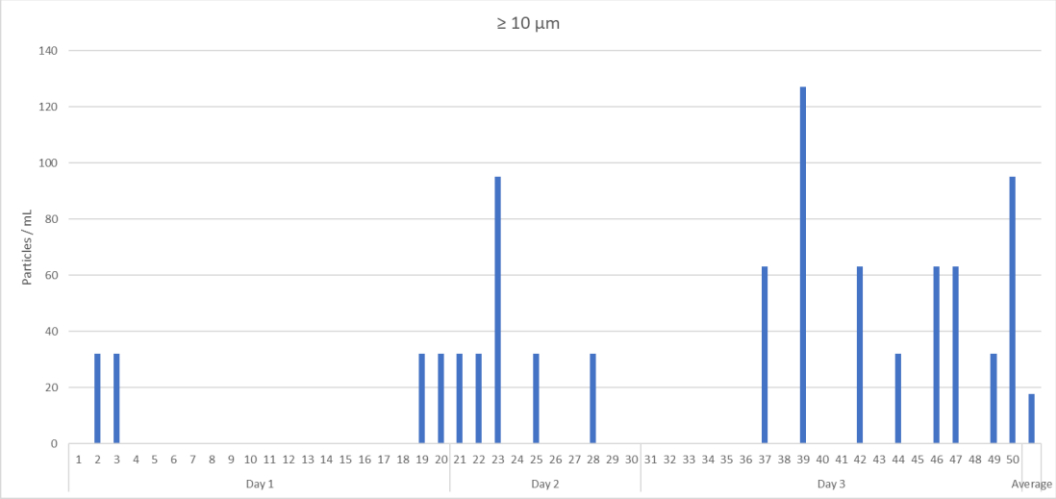

Figure 4.2: HORIZON VUE results for particles with an equivalent diameter ≥ 10 µm

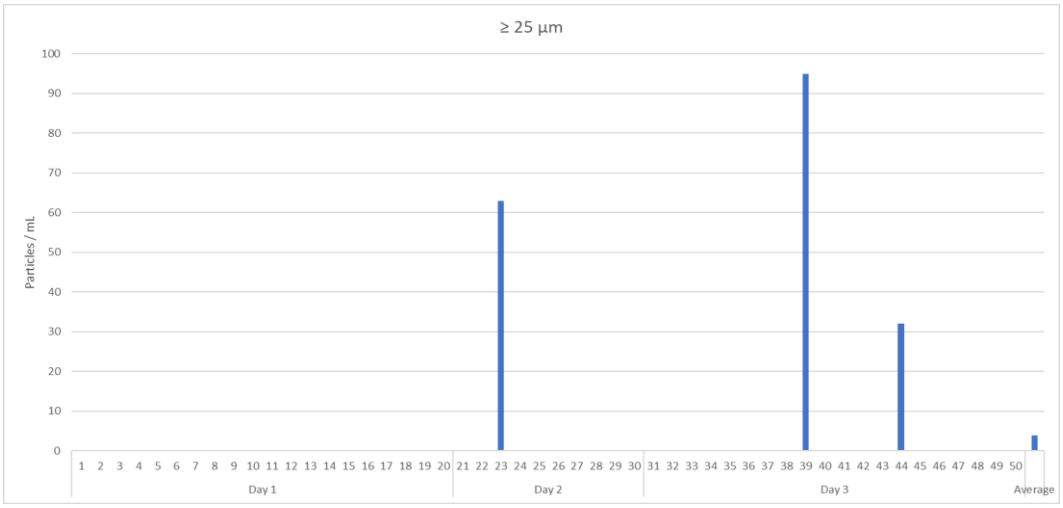

Figure 4.3 HORIZON VUE results for particles with an equivalent diameter ≥ 25 µm

4.1.2 HIAC

The next figures are the representation of the results of the sample evaluation with HIAC. The numerical results obtained are summarized on *"Annex A1. Preliminary study results"*.

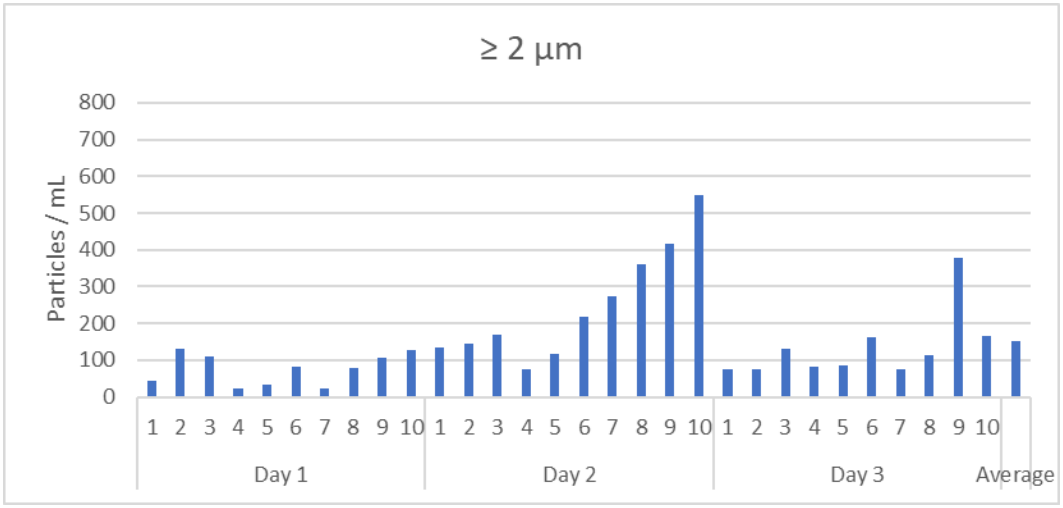

Figure 4.4: HIAC results for particles with an equivalent diameter ≥ 2 µm

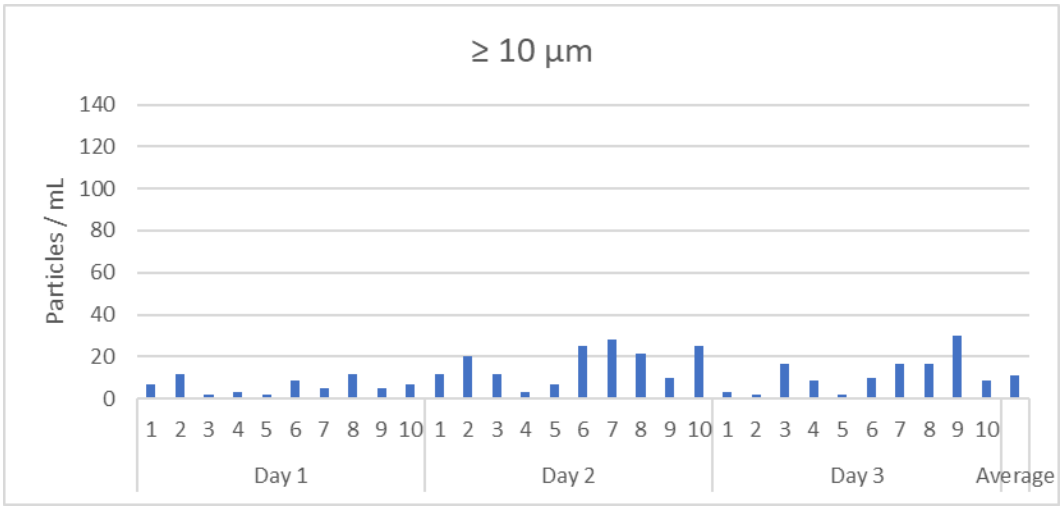

Figure 4.5: HIAC results for particles with an equivalent diameter ≥ 10 µm

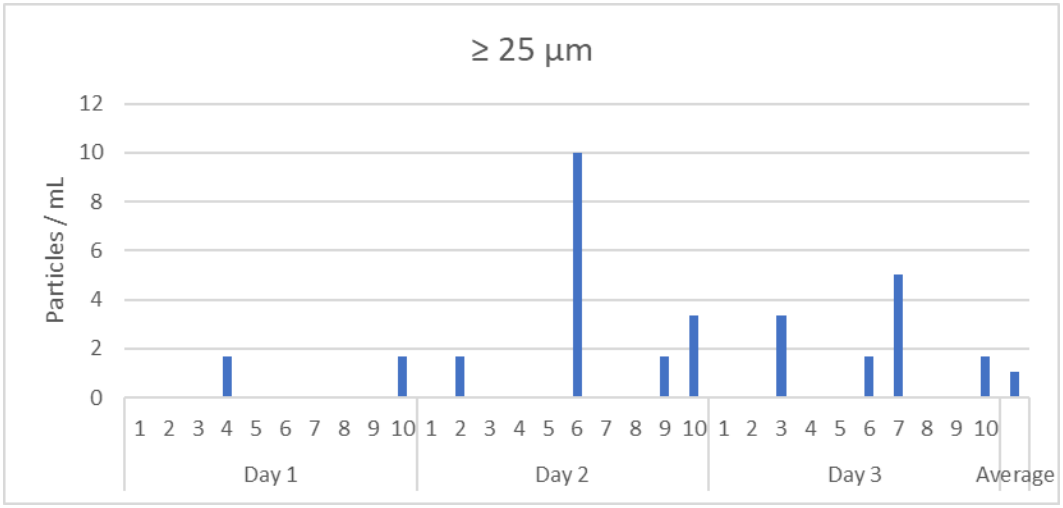

Figure 4.6: HIAC results for particles with an equivalent diameter ≥ 25 µm

4.2 Study in PFS

4.2.1 Visual assessment

During the study, any of the formulations presented any visual change in any of the time points of analysis. The appearance of all the buffers in all the points of the study is a transparent liquid without visible particles and no viscous.

The following figures show the visual evolution of the samples at all time points.

Figure 4.7: Visual assessment formulation 1

Figure 4.8: Visual assessment formulation 2

Figure 4.9: Visual assessment formulation 3

Figure 4.10: Visual assessment formulation 4

Figure 4.11: Visual assessment formulation 5

4.2.2 pH

The next figure shows the pH evolution throughout the study. In this representation is shown that the pH of each formulation was maintained constant during the study. The values obtained in each of the measurements and the average of them in each time point can be found in *"Annex A2. Study in PFS results"*.

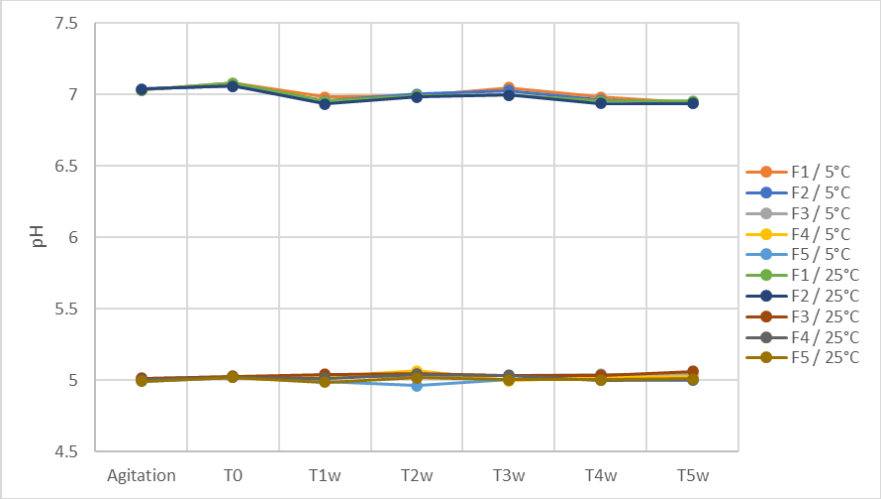

Figure 4.12: pH evolution

4.2.3 Osmolarity

The evolution of the osmolarity during the different time points of the study is summarized in the next figure. It is shown that the evolution of this parameter can be considered constant at all the time points. The values for each of the measurements and the average of them are found in *"Annex A2. Study in PFS results"*.

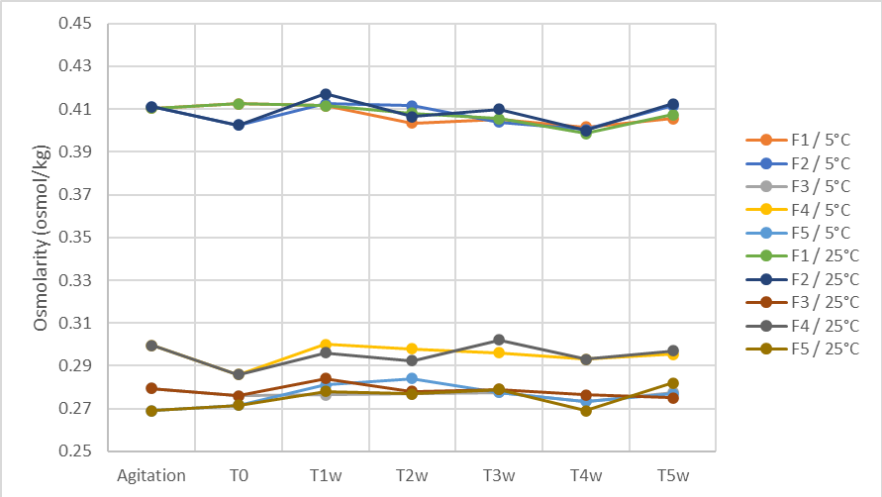

Figure 4.13: Osmolarity evolution

4.2.4 HORIZON VUE

In the next tables it is shown the average of the HORIZON VUE measurements results. The values directly obtained from the device can be found on "*Annex A2. Study in PFS results*".

Table 4.1: HORIZON VUE results average for phosphate-based formulations (particle/mL)

	F1			F2		
	>2 µm	**>10 µm**	**>25µm**	**>2 µm**	**>10 µm**	**>25µm**
T0	323.6	38.2	25.6	298.20	69.80	44.60
Agitació	1212.80	76.20	6.40	539.40	31.80	12.80
T1 / 5°C	423.33	10.67	0.00	211.67	21.33	0.00
T2 / 5°C	412.67	42.33	10.67	423.00	21.33	0.00
T3 / 5°C	325.25	39.50	0.00	1460.20	75.80	12.80
T4 / 5°C	133.00	19.00	6.40	95.40	0.00	0.00
T5 / 5°C	412.60	12.80	6.40	88.80	0.00	0.00
T1 / 25°C	529.00	63.67	42.33	582.00	10.67	0.00
T2 / 25°C	486.67	0.00	0.00	730.00	116.00	31.67
T3 / 25°C	685.60	32.00	6.40	526.80	31.60	0.00
T4 / 25°C	387.20	19.00	0.00	114.20	12.60	0.00
T5 / 25°C	450.80	44.40	6.40	101.60	12.60	0.00

Table 4.2: HORIZON VUE results average for acetate-based formulations (particle/mL)

	F3			F4			F5		
	>2 µm	**>10 µm**	**>25µm**	**>2 µm**	**>10 µm**	**>25µm**	**>2 µm**	**>10 µm**	**>25µm**
T0	508.00	108.00	44.20	260.00	31.80	19.20	647.40	171.40	69.80
Agitació	260.00	25.20	6.40	1199.80	19.20	6.40	184.00	6.40	0.00
T1 / 5°C	275.00	21.33	0.00	381.00	31.67	0.00	264.33	10.67	0.00
T2 / 5°C	867.67	21.00	0.00	560.67	31.67	0.00	402.00	10.67	10.67
T3 / 5°C	520.40	25.60	0.00	433.67	10.67	0.00	433.67	42.33	21.33
T4 / 5°C	336.20	6.40	6.40	152.20	12.60	0.00	88.80	0.00	0.00
T5 / 5°C	247.40	12.80	6.40	114.20	12.80	12.80	196.80	6.40	0.00
T1 / 25°C	1185.00	10.67	0.00	317.67	10.67	10.67	327.67	10.67	0.00
T2 / 25°C	603.00	603.00	31.67	433.67	52.67	31.67	370.33	10.67	0.00
T3 / 25°C	990.40	120.60	19.00	1085.60	19.20	6.40	804.33	32.00	21.33
T4 / 25°C	349.20	19.20	0.00	355.60	6.40	0.00	146.00	12.80	0.00
T5 / 25°C	412.60	6.40	0.00	209.40	12.80	0.00	108.00	19.00	0.00

4.2.5 HIAC

The following tables show the average of the results obtained from the sample analysis done with HIAC at each time point. The results of all HIAC measurements done can be found in *"Annex A2. Study in PFS results"*.

Table 4.3: HIAC results average for phosphate-based formulations (particle/mL)

	F1			F2		
	>2 µm	**>10 µm**	**>25µm**	**>2 µm**	**>10 µm**	**>25µm**
T0	214.17	10.83	1.67	143.34	9.17	0.00
Agitation	896.67	39.17	1.67	93.33	4.17	0.00
T1 / 5°C	256.67	12.50	2.50	124.17	6.67	1.67
T2 / 5°C	245.00	4.17	0.00	106.67	5.84	0.00
T3 / 5°C	270.00	12.50	0.84	496.67	9.17	0.00
T4 / 5°C	213.34	6.67	0.00	78.33	6.67	0.00
T5 / 5°C	205.83	24.17	0.00	131.67	0.84	0.00
T1 / 25°C	534.17	16.67	0.00	535.84	9.17	0.00
T2 / 25°C	467.50	10.00	0.00	730.00	7.50	0.00
T3 / 25°C	1088.34	39.17	0.84	74.17	0.00	0.00
T4 / 25°C	284.17	5.83	0.00	110.00	6.67	0.84
T5 / 25°C	629.17	22.50	0.00	251.67	3.33	0.84

Table 4.4: HIAC results average for acetate-based formulations (particle/mL)

	F3			F4			F5		
	>2 µm	**>10 µm**	**>25µm**	**>2 µm**	**>10 µm**	**>25µm**	**>2 µm**	**>10 µm**	**>25µm**
T0	143.34	7.50	0.84	123.33	7.50	0.00	119.17	5.84	0.00
Agitation	295.83	8.34	0.84	121.67	11.67	2.50	45.00	2.50	0.00
T1 / 5°C	152.50	14.17	0.84	129.17	7.50	2.50	69.17	12.50	0.84
T2 / 5°C	141.67	5.00	0.00	145.84	5.00	1.67	97.50	6.67	0.00
T3 / 5°C	107.50	6.67	0.00	573.33	30.00	0.84	65.83	5.00	0.00
T4 / 5°C	393.33	15.00	0.00	186.67	15.00	2.50	45.84	6.67	0.00
T5 / 5°C	422.50	28.34	0.84	105.84	4.17	0.00	104.17	24.17	1.67
T1 / 25°C	1163.17	72.50	0.84	668.33	45.00	0.00	305.00	41.67	1.67
T2 / 25°C	597.50	23.33	0.00	686.67	28.34	0.00	181.67	12.50	0.00
T3 / 25°C	274.17	15.00	0.00	890.83	41.67	0.84	184.17	9.17	0.00
T4 / 25°C	365.84	19.17	0.00	355.00	19.17	0.84	474.17	97.50	0.00
T5 / 25°C	416.67	20.00	1.67	859.17	41.67	0.84	135.00	6.67	0.00

5 Discussion

5.1 Preliminary study

5.1.1 Device variability

To determine the variability in the measure of each of the devices used, all the results obtained during the 3 days of analysis are considered together. This allows considering the variation of the external conditions in the variability study.

For the study of both devices, are considered all the particles with an equivalent diameter equal or larger than 2 µm. This particle size is the lower size regulated by the Pharmacopeia for injections and parentals, the field in which this study is developed.

To study the variability of both devices, the first thing done is to determine if the distribution of the results can be approached to a normal distribution. In case they can be approached to this statistical model, it is possible to directly calculate the sample average and standard deviation. Finally, to obtain a confidence interval, it must be specified a significance level of the confidence interval, and this can be calculated with the equation below**.**

$$\text{Confidence interval} = \left(\overline{\text{X}} \pm \text{Z}\propto_{/2} \frac{\sigma}{\sqrt{\text{N}}}\right) \qquad \textbf{Equation 7}$$

Where "$\bar{X}$" represents the average, "$Z\propto_{/2}$" represents the tabular number from the normal distribution N (0, 1), "σ" represents the standard deviation and "N" is the number of tests of the sample.

For both devices, it's used a significance level equal to 5% giving a confidence interval of 95%. With this requisite, the "$Z\propto_{/2}$" value obtained from the normal distribution is 1,960.

HORIZON VUE variability

The next figure shows the distribution of the HORIZON VUE results. At the x-axis is represented the particle count (≥ 2µm) obtained (in intervals pf 10 particles) and at the y-axis is represented the number of times the test result is inside that range.

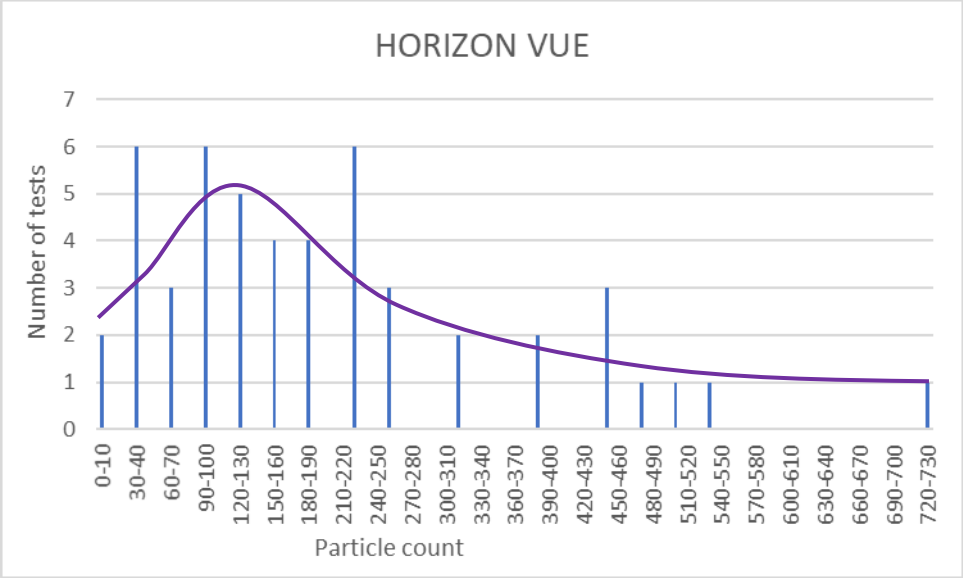

Figure 5.1: HORIZON VUE results distribution

As it is shown, the distribution of the measures can be approached as a normal distribution. Once this first approach is accepted, the average and the standard deviation of the sample are calculated using the *MS Excel* functions *AVERAGE* and *STDEV.S* respectively. From this calculation is obtained an average of 201,16 particles/mL and a standard deviation of 160,11.

With these results, the confidence interval can be calculated using the equation "7".

$$Confidence\ interval_{\ HORIZON\ VUE} = \left(201{,}16 \pm\ 1{,}960\,\frac{160{,}11}{\sqrt{50}}\right) \qquad \textbf{Equation 8}$$

$$Confidence\ interval_{\ HORIZON\ VUE} = (201{,}16 \pm 44{,}38\ ) \qquad \textbf{Equation 9}$$

To obtain some final value that can be comparable with measurement from other samples, is calculated this variation as a percentage of the average.

$$\%error = \frac{44{,}38}{201{,}16} * 100 = 22\% \qquad \textbf{Equation 10}$$

Finally, the percentage of error of the average with a level of confidence of 95% obtained for HORIZON VUE measures is of 22% over the average.

HIAC variability

The next figure shows the distribution of the HIAC results. At the x-axis is represented the particle count (≥ 2µm) obtained (in intervals pf 10 particles) and at the y-axis is represented the number of times the test result is inside that range.

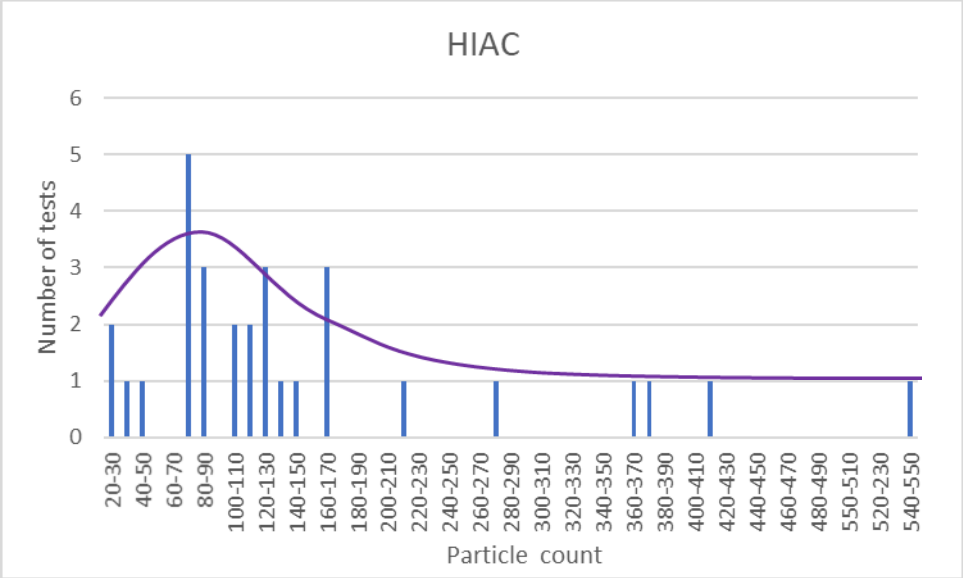

Figure 5.2: HIAC results distribution

Considering the distribution shown in the figure above, the distribution of the measures can be approached as a normal distribution. Once this first approach is accepted, the average and the standard deviation of the sample are calculated using the *MS Excel* functions *AVERAGE* and *STDEV.S* respectively. From this calculation is obtained an average of 151,93 particles/mL and a standard deviation of 123,32.

With these results, the confidence interval can be calculated using the equation "7".

$$Confidence\ interval_{HIAC} = \left(151{,}93 \pm 1{,}960\frac{123{,}32}{\sqrt{30}}\right) \quad \textbf{Equation 11}$$

$$Confidence\ interval_{HIAC} = (151{,}93 \pm 44{,}84) \quad \textbf{Equation 12}$$

In the same way as it has been done with HORIZON VUE, the variation is calculated as a percentage above the average.

$$\%error = \frac{44{,}84}{151{,}93} * 100 = 30\% \quad \textbf{Equation 13}$$

Finally, the percentage of error of the average with a level of confidence of 95% obtained for HIAC measures is 30% over the average.

5.1.2 Device comparation

To be able to consider the results obtained from the two devices are comparable between them, the samples used for both devices were obtained from the same homogenized volume. In this case, the study is done for 3 range of particle size (≥ 2µm, ≥ 10 µm and ≥ 25 µm) which are the three ranges regulated in the industrial process.

When thinking about comparing devices, the first criterion that comes to mind is the comparison between the average obtained from each device. These averages are calculated considering all the results obtained during the 3 days of analysis. The averages obtained and the standard deviation of each size and device are summarized in the next table.

Table 5.1: Average and standard deviation results

		HORIZON VUE		HIAC		Difference
		Average	**Standard deviation**	**Average**	**Standard deviation**	**Average**
Particle size	**≥ 2 µm**	201.16	160.11	151.93	125.32	49.23
	≥ 10 µm	17.78	30.13	11.28	8.35	6.50
	≥ 25 µm	3.8	16.47	1.06	2.12	2.74

With these results, it isn't possible to determine if the results represent statistically the same or if it exists some difference. Even so, it's possible to calculate the confidence interval for the 3 ranges of particle size equally as explained in the previous section (4.1 Device variability), a parameter that can provide the first approach. Thus, the intervals obtained are shown in the following table and represented in the figure below.

Table 5.2: Confidence intervals

	HORIZON VUE (n= 50)			HIAC (n= 30)		
	≥ 2 µm	**≥ 10 µm**	**≥ 25 µm**	**≥ 2 µm**	**≥ 10 µm**	**≥ 25 µm**
Error	44.38159	8.352131	4.565975	44.84	2.99	0.76
Low bound	156.7784	9.427869	-0.76598	107.0894	8.2918	0.29702
High bound	245.5416	26.13213	8.365975	196.7793	14.26553	1.81498

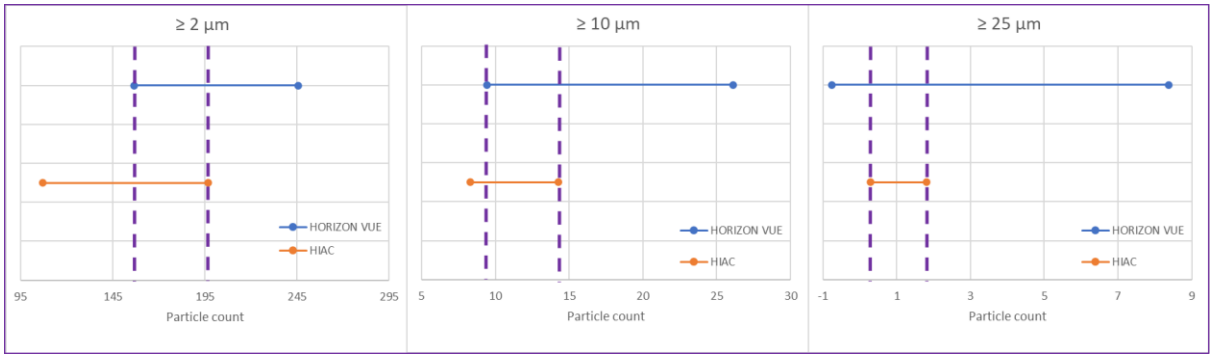

Figure 5.3: Confidence intervals and coincident zone representation

Analyzing the obtained intervals, it is shown that, for all the particle size ranges, there is a coincident zone – represented between the purple lines –. This observation supports the hypothesis that the results from both devices can be considered statistically equal. Even so, to be able to affirm that statistically there is no difference between both devices, it is studied by the comparison of averages in normal populations test.

Comparison of averages in normal populations test

For this test 2 hypotheses must be defined. The first one is the starting hypothesis (H0) and is the one that will be verified or discarded in the test. The other hypothesis is the alternative hypothesis (H1) and is the one accepted in case the starting hypothesis is discarded. In this study:

- H_0: The averages of HORIZON VUE and HIAC measurements are equal. ($\overline{X_1} - \overline{X_2} = 0$)
- H_1: The averages of HORIZON VUE and HIAC measurements are different. ($\overline{X_1} - \overline{X_2} \neq 0$)

Where "$\overline{X_1}$" is the average of measurement with HORIZON VUE and "$\overline{X_2}$" is the average of measurement with HIAC.

Once the hypotheses are defined, they must be set at a significance level. In this study, it is taken a significance level of 5% obtaining results with a level of confidence of the 95%.

Since the sample size is equal to or larger than 30 tests in both cases, both are treated as big samples. As consequence, it must be used the big sample normal distribution. Considering the significance level selected and the sample size, the "$Z_{\propto/2}$" obtained from the normal table, in this case, is equal to 1,960.

To verify or discard the starting hypothesis, it must be calculated a "Z" value based on the results

obtained from the different samples. For this calculation is used the next equation.

$$Z = \frac{\overline{x_1} - \overline{x_2}}{\sqrt{\frac{{\sigma_1}^2}{n_1} + \frac{{\sigma_2}^2}{n_2}}}$$ **Equation 14**

Where "$\bar{x}$" represents the average, "σ" represents the standard deviation and "n" is the number of tests of the sample. The subindex "1" refers to the HORIZON VUE and the subindex "2" refers to the HIAC.

By subtracting the values shown in "table 5.1" in the equation "14", are obtained the Z values summarized in "table 5.3" for each of the 3 particle size ranges. If this calculated Z value is shorter than the one obtained from the normal distribution, the starting hypothesis is verified. Otherwise, the starting hypothesis is refused, and the alternative hypothesis is accepted.

Table 5.3: Z and $Z_{\alpha/2}$ values and hypothesis decision

	Particle size		
	≥ 2 µm	**≥ 10 µm**	**≥ 25 µm**
$Z_{\alpha/2}$	1.960	1.960	1.960
Z	1.529	1.437	1.162
$Z < Z_{\alpha/2}$	Si	Si	Si
Accepted hypothesis	H_0	H_0	H_0

As it's shown in the table above, the starting hypothesis is accepted for all the particles size, which means that, statistically the result obtained from both devices are equal and represent the same population.

5.2 Study in PFS

Before the discussion of the results needed to accomplish the objectives set at the beginning of the study, it is necessary to check, using the control parameters, that no sample shows any evidence that some unexpected reaction has occurred. These control parameters are the visual assessment, the pH, and the osmolarity.

Referring to the visual assessment, it has been proved that any of the samples have shown any difference from the beginning of the study.

As it's shown in the pH and osmolarity results representation, both parameters can be considered constant during al the study. To quantify this small variation in both parameters it has been calculated the percentage of variation in each time point over the value obtained at time 0. The two tables below summarize the obtained percentage of variation.

Table 5.4: pH variation (percentage above time 0 pH)

pH % variation	Agitation	T1w	T2w	T3w	T4w	T5w
F1 / 5°C	-	-1.36%	-1.26%	-0.45%	-1.37%	-1.90%
F2 / 5°C	-	-1.46%	-0.79%	-0.45%	-1.38%	-1.70%
F3 / 5°C	-	-0.02%	-0.05%	0.01%	0.22%	0.23%
F4 / 5°C	-	0.08%	0.87%	-0.48%	-0.02%	0.05%
F5 / 5°C	-	-0.55%	-1.18%	-0.34%	-0.34%	-0.43%
F1 / 25°C	-0.68%	-1.75%	-1.22%	-1.17%	-1.74%	-1.77%
F2 / 25°C	-0.27%	-1.75%	-1.09%	-0.89%	-1.69%	-1.71%
F3 / 25°C	-0.34%	0.23%	0.29%	0.04%	0.13%	0.69%
F4 / 25°C	-0.34%	-0.16%	0.42%	0.29%	-0.42%	-0.38%
F5 / 25°C	-0.56%	-0.67%	-0.09%	-0.33%	-0.31%	-0.23%

Table 5.5: Osmolarity variation (percentage above time 0 osmolarity)

Osmolarity % variation	Agitation	T1w	T2w	T3w	T4w	T5w
F1 / 5°C	-	-0.24%	-2.18%	-1.82%	-2.67%	-1.70%
F2 / 5°C	-	2.48%	2.24%	0.37%	-0.50%	2.24%
F3 / 5°C	-	0.18%	0.36%	0.54%	-0.91%	0.54%
F4 / 5°C	-	4.90%	4.20%	3.50%	2.45%	3.32%
F5 / 5°C	-	3.50%	4.60%	2.21%	0.74%	2.03%
F1 / 25°C	-0.48%	-0.24%	-1.09%	-1.70%	-3.39%	-1.21%
F2 / 25°C	2.11%	3.60%	0.99%	1.86%	-0.62%	2.48%
F3 / 25°C	1.27%	2.90%	0.72%	1.09%	0.18%	-0.36%
F4 / 25°C	4.72%	3.50%	2.27%	5.59%	2.45%	3.85%
F5 / 25°C	-0.92%	2.39%	2.03%	2.76%	-0.92%	3.87%

In the case of the pH, the largest difference from the value measured in time 0 is 1,90% and in the case of the osmolarity, is 5,59%. In both cases, the value is below 10% so this variation can be attributed to the instrumental error, and it is proved that the parameters are maintained constant.

Considering the evolution of the three parameters throughout the study, all the samples are considered valid, and it is possible to proceed with the discussion of the results referent to the main purposes of the study.

5.2.1 Subvisible particles evolution

To study the evolution along the time of the particles found in the solution, the results used are the ones obtained with the device which bases his measurement in LO. This decision is taken because this analytical method is the one accepted by the European Pharmacopeia for the subvisible particle determination, because it allows analyse a larger volume of the sample, because the analytical process is simpler and has less steps and this make it less prone to suffer some external contamination and because, based on the preliminary study done, both devices give results statistically equals.

The study of the possible interaction between the formulations with the silicone oil inside the PFS is focused on two main aspects: the time and the temperature in which the PFS has been stored. In this study is supposed that the particle count increase is due to the silicone oil in the PFS. In the same way, understanding that the only source of particles studied is the silicone oil, the only particle size range of interest is the smallest because is in the one where the silicone oil particles can be found. The variation in the other ranges is attributed to the instrumental variability.

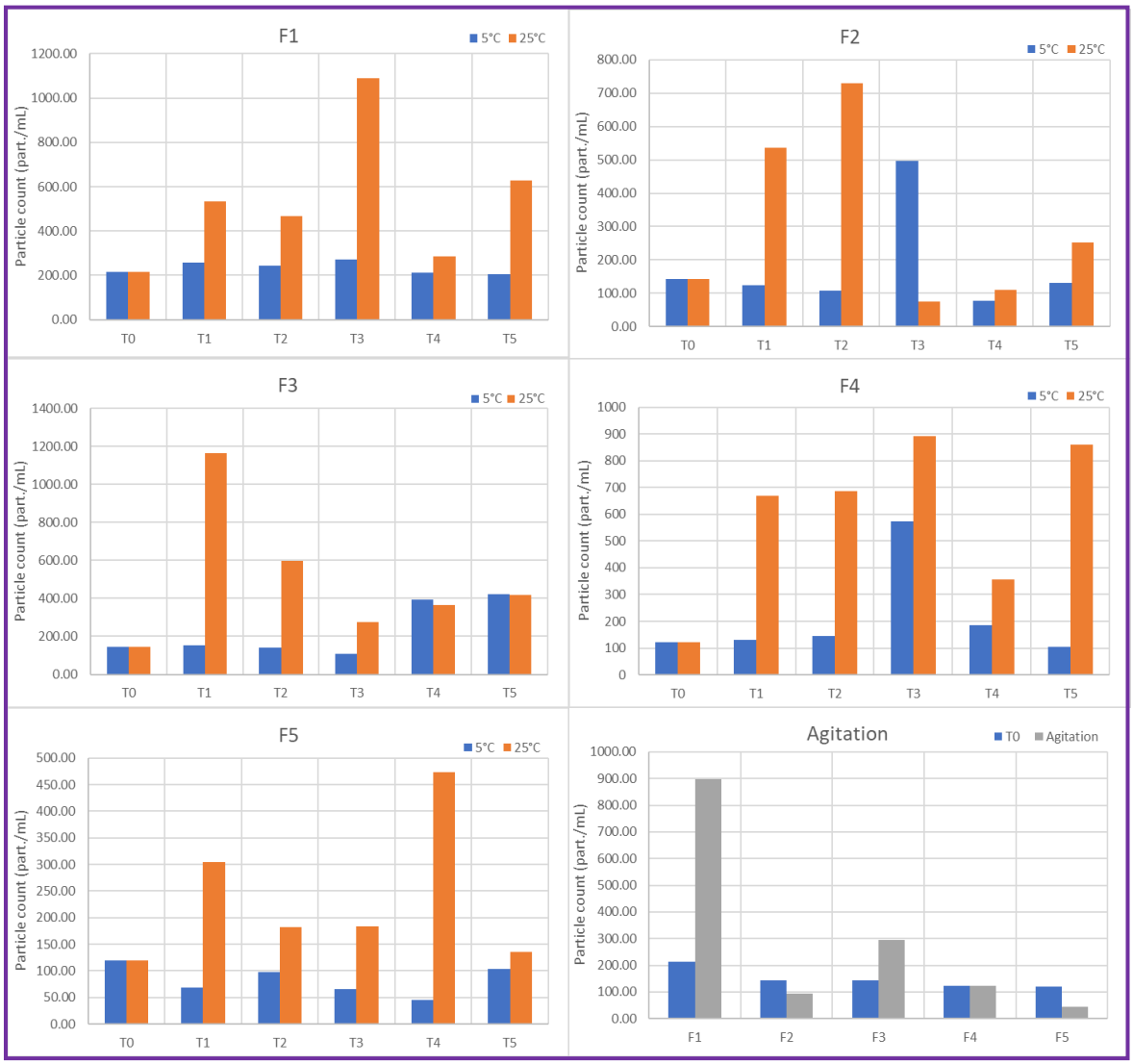

Figure 5.4: HIAC results at different time points of analysis

In the figure above is possible to see the representation of the results obtained for each formulation throughout the study. The blue columns refer to the samples stored at 5°C and the oranges refer to the ones stored at 25°C. Figure 8 shows that the samples stored at 5°C have, in general, a different behaviour than those stored at 25°C. The last graphic (blue-grey) shows the result for the samples submitted to the agitation in comparison with the results of the same formulation at time zero.

Except for the results of the formulations 2 and 4 in the third week, it is shown that the particle count of the samples stored at 5°C are almost constant respectively for each formulation and the small variation between the different weeks can be attributed to the instrumental variability. For the 2 samples that don't present this stability at 5°C, a possibility is that they were contaminated during the process between taking the sample of the PFS and analysing it or the possibility that the PFS used for that time point had a defect that made grow the particles in an unexpected way. But, with the information available is not possible to conclude the real origin of this increment.

When analysing the orange columns – referents to the samples stored at 25°C – no general trend is discernible. In all the formulations at almost all the time points, the result obtained is bigger than the result obtained from the samples at 5°C, but this increase doesn't follow any trend or describable behaviour.

Analysing the results of the samples after 24 hours of agitation, it can be observed an increase in the formulations 1 and 3 but much bigger for the first them. Formulations 2 and 5 present a lower number of particles after the agitation and formulation 4 maintained almost constant. An interesting fact found in these results is that the 2 solutions that have PS20 (100 ppm) have increased the particle count, the 2 that have P188 with a concentration of 200 ppm have decreased the particle count and the only formulation that has P188 with a concentration of 4000 ppm is the only one that maintained constant. Even, with these results, is not a conclusive affirmation, it is interesting to notice that relation.

Considering these observations, it could be assumed that storing the samples at 5°C help to maintain constant the number of particles found inside the PFS limiting, to almost none, the interaction between the formulation and the silicone oil. On the other side, it seems that storing the PFS at 25°C can generate a random effect on the particle count.

5.2.2 Device comparation

For the comparison between the results obtained with both devices, is used the T-Student test. This allows comparing the results of 2 samples to verify if their average represents the same population, understood as equivalent results for both devices. This test is suitable when the results present a normal distribution and when each sample has a size smaller than 30. In this study, the number of tests of each group studied (each formulation at each time point) is small and it's not possible to prove that they follow a normal distribution, but this characteristic was studied and accepted in the Preliminary study done.

For this test 2 hypothesis must be defined. The first one is the starting hypothesis (H0) and is the one that will be verified or discarded in the test. The other hypothesis is the alternative hypothesis (H1) and is the one accepted in case the starting hypothesis is discarded. In this study:

- H_0: The averages of HORIZON VUE and HIAC measurements are equal. ($\overline{X_1} - \overline{X_2} = 0$)
- H_1: The averages of HORIZON VUE and HIAC measurements are different. ($\overline{X_1} - \overline{X_2} \neq 0$)

Where "$\overline{X_1}$" is the average of the HORIZON VUE measurements and "$\overline{X_2}$" is the average of the HIAC measurements.

After defining the hypothesis, the significance level must be set. In this study, it is taken a significance level of 5% obtaining results with a level of confidence of the 95%.

Once defined the significance level and knowing that the degrees of freedom of the system is defined as shown in the next equation, in the table of T-Student it can be found the value of the parameter $t_{tabular}$.

$$DoF = n_1 + n_2 - 2 \qquad \textbf{Equation 15}$$

Where "DoF" are the degrees of freedom of the system, "n1" is the number of tests done with HORIZON VUE and "n2" are the number of tests done with HIAC.

This is a constant number of 5 DoF. Although at the beginning of the study, had less HORIZON VUE, some samples were accidentally contaminated so they can't be used leaving 3 degrees of freedom for those samples.

Considering the confidence level set and the degrees of freedom, it's possible to obtain the table a $t_{tabular}^{DoF=5}$ = 2,5706 and $t_{tabular}^{DoF=3}$ = 3,1824.

To complete the T-Student test is also needed to calculate a t based on the results from both devices. This parameter is calculated as it's shown below.

$$t = \frac{\overline{X_1} - \overline{X_2}}{\sqrt{\frac{{S_c}^2}{n_1} + \frac{{S_c}^2}{n_2}}} \qquad \textbf{Equation 16}$$

Where "$\overline{\boldsymbol{x_i}}$" is the average of the tests done with each device, "$\boldsymbol{n_i}$" is the number of tests done with each device and "$\boldsymbol{{S_c}^2}$" is calculated with the standard deviations of the samples ("$\boldsymbol{S_i}$") as shown in equation "8". The subindex "1" refers to the HORIZON VUE and the subindex "2" refers to the HIAC.

$${S_c}^2 = \frac{(n_1 - 1){S_1}^2 + (n_2 - 1){S_2}^2}{n_1 + n_2 - 2} \qquad \textbf{Equation 17}$$

After doing these calculations for each formulation at each time point of the study, are obtained the t calculated values summarized in the tables below. These calculated t values are compared with the tabular to accept or refuse the starting hypothesis in each case. If the $t_{tabular}$ ($t_{tabular}^{DoF=5}$ = 2,5706 or $t_{tabular}^{DoF=3}$ = 3,1824) is larger than the calculated t (in absolute amounts), H_0 is accepted otherwise, H_0 is refused and accepted H_1.

In the next tables are shown in black the ones where H_0 is accepted and in red the ones where H_1 is accepted.

Table 5.6: T values calculated with HORIZON VUE and HIAC results (particles ≥2 µm)

	F1	F2	F3	F4	F5
T0	1.7722	0.7015	2.6454	1.3125	1.8371
Agitation	0.6646	3.1291	-0.4289	1.0863	1.7733
T1 / 5°C	2.1787	1.6517	2.4785	1.2262	3.5063
T2 / 5°C	4.0348	6.2982	2.6158	2.6890	1.3015
T3 / 5°C	0.2640	2.3633	2.8447	-1.6490	6.6348
T4 / 5°C	-0.8978	0.2310	-0.2574	-0.3897	0.5789
T5 / 5°C	1.2244	-0.9192	-1.5201	0.2396	1.1909
T1 / 25°C	-0.0284	0.5337	0.0541	-5.5943	0.2730
T2 / 25°C	0.2342	0.0000	0.0722	-2.2918	3.0537
T3 / 25°C	-2.4703	4.1174	3.0854	0.5164	6.3195
T4 / 25°C	1.3213	0.0402	-0.0832	0.0032	-5.6666
T5 / 25°C	-2.3478	-4.8534	-0.0259	-3.1099	-0.6241

Table 5.7: T values calculated with HORIZON VUE and HIAC results (particles ≥10 µm)

	F1	F2	F3	F4	F5
T0	2.6170	0.8657	1.4695	0.8372	3.3597
Agitation	0.8569	1.6572	0.6516	0.5732	0.3614
T1 / 5°C	-0.1299	1.0609	0.5200	1.0289	-0.1330
T2 / 5°C	2.8580	1.1243	0.5902	1.1357	0.2860
T3 / 5°C	0.7590	5.0775	1.7676	-1.3205	2.7866
T4 / 5°C	0.5836	-7.5650	-0.8030	-0.1137	-2.5210
T5 / 5°C	-0.8660	-1.8898	-1.1738	0.6580	-1.6468
T1 / 25°C	0.7497	0.1077	-2.9795	-2.4932	-2.2514
T2 / 25°C	-4.0290	2.1994	0.2031	0.6510	-0.1330
T3 / 25°C	-1.4774	0.9442	1.7836	-1.5497	12.2519
T4 / 25°C	0.6222	0.2812	0.0026	-1.1675	-3.2534
T5 / 25°C	0.8118	0.4397	-1.2699	-2.1958	0.5834

Table 5.8: T values calculated with HORIZON VUE and HIAC results (particles ≥25 µm)

	F1	F2	F3	F4	F5
T0	2.2275	0.9041	2.0604	1.4639	2.2604
Agitation	0.4407	0.9759	0.5192	0.3639	0.0000
T1 / 5°C	-1.3416	0.0000	-1.3416	-4.0411	-1.3416
T2 / 5°C	0.7746	0.0000	0.0000	0.0000	0.7746
T3 / 5°C	-1.8898	0.9759	0.0000	-1.3416	1.5492
T4 / 5°C	0.5976	0.0000	0.5976	-1.8898	0.0000
T5 / 5°C	0.5976	0.0000	0.5192	0.9759	-1.8898
T1 / 25°C	0.7746	0.0000	-1.3416	0.7746	0.0000
T2 / 25°C	0.0000	1.3487	0.7746	1.3487	0.0000
T3 / 25°C	0.5192	0.0000	0.8994	0.5192	1.5492
T4 / 25°C	0.0000	-1.8898	0.0000	-1.8898	0.0000
T5 / 25°C	0.5976	-1.8898	-1.8898	-1.8898	0.0000

With a first view of the tables above is easy to suspect that there is a difference in the acceptance of H_0 between the different particle size ranges. That is appreciable because, in the smallest particle range (≥2µm), it can be found in all formulations at different time points samples where H_0 is refused to contrast with the largest particle size (≥ 25µm) where H_0 is refused in only one sample of all the study.

To quantify the acceptance obtained of the starting hypothesis that defend that the 2 devices obtain equal results with a 95% of confidence, is calculated the percentage of samples accepted for each particle size range. Also is calculated the global acceptance percentage considering all the values obtained. The results obtained from this quantification are summarized in the table below.

Table 5.9: H_0 acceptance

	≥ 2 µm	≥ 10 µm	≥ 25 µm	Global
Number of samples where H_0 is accepted	46	53	59	158
Total number of samples	60	60	60	180
Acceptance %	77%	88%	98%	88%

6 Conclusions

The main conclusions of this study can be summarized as follows:

The first purpose of the study was to develop an evaluation process to determine the capability of two different devices to determine subvisible particles in a solution. In doing so, a variability study with a 95% of confidence in each device and a comparison between them was performed. Results revealed that the confidence interval was 151,93 ± 44,84 part/mL and 201,16 ± 44,38 part/mL for HIAC and HORIZON VUE devices respectively. This represents an error of 30% and 22% above the average. It's important to highlight that these values are only applicable to the studied solution. *Preliminary study* demonstrated that both can be considered statistically equal with a 95% of confidence for the 3 particle-size ranges studied: ≥2 µm, ≥10 µm and ≥25 µm. With the *Study in PFS* 77%, 88% and 98% of the samples with a particle-size of ≥2 µm, ≥10 µm and ≥25 µm respectively validated the hypothesis that both can be considered statistically equal. Although two of the three percentages (samples with particle size ≥2 µm, ≥10 µm) are below 95%, it can be considered high enough taking into account that part of the samples was measured during the training period onmethods.

The second purpose was to study the effect of silicone oil in PFS solutions during the three different storage conditions. The group of PFS stored at 5 presented a minimal interaction between the silicone oil and the formulation, maintaining almost constant the amount of subvisible particles found for all the study. Regarding PFS stored at 25°C and subjected to 24 hours of mechanical stress, results showed random behaviour consequently, is not possible to define any general trend. Finally, PFS. In this sense, storage at 5°C was concluded to be the best condition to prevent the increase of the subvisible particles in PFS solutions.

Results achieved in this work can't be considered as a final conclusive statement, however, they can be understood as a significant first approach.

As a personal growth, this study has allowed me to experience a real working environment in the field of research. During my time there, I have been able to put into practice the skills I learned during my apprenticeship while greatly improving my laboratory skills. Being surrounded by such a professional environment, I learned how a complex research study is conducted and how to adapt to possible changes and unexpected situations.

7 Environmental impact

The next section consists of a global evaluation of the environmental impact generated during the development of the present study.

To perform the present study was used a total volume of 0,55 L of the different formulations (50mL for the preliminary study and 100 mL of each of the 5 formulations for the study in PFS) were and any of the chemicals used in all the formulations are considered dangerous for the environment. Because of the low concentration of all of them and the small amount used, the environmental impact generated by the solutions can be considered depreciable.

Most of the material used for the sample preparation and analysis, such as flasks, beakers, spatulas, and other laboratory utensils, can be reused after the appropriate cleaning – and sterilization if needed – procedure. This reduces the number of residues generated during the study to the single-use materials like safety globes, pre-filled syringes, vials, and pipette tips. These single-use materials were classified and placed in an adequate container following the waste classification established in the laboratory where the study was performed.

Considering the solutions and the material used, the environmental impact attributable to the study because of the physical waste generated could be considered negligible. In addition to the physical waste, it also should be considered the impact generated by obtaining the electricity needed to supply to all the devices involved in the analysis.

Vials and ampoules used to supply parenteral drugs are usually overfilled (25% more than needed) to ensure that the final user receives the required dose, the thing that can be avoided using PFS charged by the manufacturer with the exact dose. When this study is understood as part of the research process to progress in PFS technology and considering all the drug volume that could be saved if is used PFS as an alternative to vials, the impact of used material and energy for the study can be considered negligible and the results of the whole research process can produce to a positive impact producing much less to supply the same number of doses.

8 Economic evaluation

In the following section, an economic evaluation is taken to have an approach of the financial resources earmarked to develop this study. This evaluation is divided in 3 parts: chemical products costs, material and installations costs and human resources costs.

8.1 Chemical products costs

In the market, chemical products are sold in some standard quantities, so it is not possible to buy only the quantity needed. In most cases, the packaging sizes are designed to provide enough to cover the needs of the laboratories in an easy-to-handle size (500g, 1kg, 2kg or 1L among other sizes). In the case of this study, the quantities required are very small, in most cases less than 1 gram. To approximate the costs that this study could generate for the laboratory where it is carried out for the use of these chemicals, it is assumed that the economic burden of the quantities used represents 5% of the selling price of the container used. This approximation covers the amount needed to prepare the formulation as well as the small amount wasted in the manufacturing process.

Table 8.1: Chemicals Costs

Component	Manufacturer	Product No.	Selling price	Applicable Cost
Acetic acid	Merk	1.00063.1000	58,80 €/L	2,94 €
Sodium acetate trihydrate	Sigma Aldrich	1.28205.1001	52,50 €/kg	2,63 €
Sodium dihydrogen phosphate monohydrate	Merk	1.06346.0500	46,40 €/500g	2,32 €
di-Sodium hydrogen phosphate heptahydrate	Sigma Aldrich	1.06574.1000	53,00 €/kg	2,65 €
Polysorbate 20	Sigma Aldrich	8.17072.1000	78,00 €/L	3,90 €
Poloxamer 188	Merk	1.37112.1000	309,00 €/kg	15,45 €
L-Arginine HCl	Sigma Aldrich	1.01544.1000	289,00 €/kg	14,45 €
Sucrose	Pfanstiehl	S-124-2-MC	199,40 €/kg	9,97 €
Total				**54,31 €**

8.2 Material and installations costs

Different materials have been used for the development of the study. The material costs cover the single-use material used, while the reusable material used, such as beakers or flasks, are considered together with the installation costs.

As in the assessment of chemicals, for single-use materials, it is not always possible to buy the exact amount needed on the market. For this economic evaluation it is assumed that the study takes place in a laboratory where the resting material can be used for other experiments. Therefore, to calculate the costs attributed to each of the materials, the unit price is calculated based on the selling prices of the containers used. The attributed costs are calculated as shown in the following equation:

$$Attributed\ Costs\ (€) = \frac{Container\ price\ (^{€}/_{container})}{Units\ in\ the\ container\ (^{Unit}/_{Container})} * Needs\ (Units) \qquad \textbf{Equation 18}$$

Table 8.2: Material Costs

Material	Selling price	Needs	Attributed Cost
Omnifix 20 mL syringe	2,50 €/unit	10 units	25,00 €
Sartorius syringe filter 0,22µm	138,00 €/50 units	10 units	27,60 €
Fisher Scientific InVitro Biotainer	638,00 €/100 units	10 units	63,80 €
Pre-fille syringes + PFS stoppers	0,50 €/unit	360 units	180,00 €
Pipette tips 200 µL ep Dualfilter	170,00 €/10 boxes	5 boxes	85,00€
Measuring vessels for freezing point osmometer	347,00 €/ 1000 units	126 units	43,72€
3mL glass vials	77,70 €/144 units	240 units	130,00€
Total			**556,62 €**

The installation costs consist of the aggregation of the costs attributed to the use of the devices to perform the analyses of the study and the costs of the other necessary services. This service fee covers electricity and water services, as well as laboratory cleaning and reusable material used for sample preparation.

The costs attributed to the use of the devices are calculated using the following equations.

$$Monthly\ Cost\ (€/\text{month}) = \frac{Selling\ price\ (€)/Amortization\ period\ (years)}{12\ months/1\ year} \qquad \textbf{Equation 19}$$

$$Cost\ (€) = Monthly\ Cost\ (€/month) * \text{Time of use (month)} \qquad \textbf{Equation 20}$$

Table 8.3: Devices Costs

Device	Selling price	Annual amortization	Attributed Cost
Lab-pH Meter inoLab® pH 7310P	1327,15 €	11,06 €	22,12 €
Osmomat 010	7806,00 €	65,05 €	130,10 €
HIAC 9703+	13741,79 €	114,51 €	229,03 €
HORIZON	30000,00 €	250,00 €	500,00 €
Total			**881,25 €**

The service fee is derived as 20% of the costs attributed to the use of the devices.

Table 8.4: Installation Costs

Concept	Attributed Cost
Devices	881,25 €
Services	176,25 €
Total	**1057,50 €**

8.3 Human resources costs

In this economic evaluation, is considered the wage of everyone that has taken part in the study.
The total cost attributed to each of the personal involved on the study is obtained by multiplying the hours dedicated to the study by the hourly salary.

The salaries are an estimation based on the Spanish and German average salary for each of the positions that taken part in the study.

Table 8.5: Human resources costs

Person's role	Hours worked	Hourly salary	Cost
Principal researcher (trainee)	640 h	8 €/h	5120 €
Academic supervisor	80 h	40 €/h	3200 €
Company supervisor	110 h	40 €/h	4400 €
Supporting technician 1	150 h	25 €/h	3750 €
Supporting technician 2	70 h	25 €/h	1750 €
Total			**18220 €**

8.4 Total costs

The total cost of the study can be calculated as the addition all the costs mentioned previously.

Table 8.6: Total cost of the study

Type of cost	Amount
Chemicals	54,31 €
Material	554,62 €
Installations	1057,50 €
Wage	18220,00 €
Total Cost	19886,43 €

The total costs calculated to develop the study are 19886,43 €. This results a final quote of the study of 19900 €.

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Annex A: Results

A1. Preliminary study results

HORIZON VUE

Table A.1: HORIZON VUE obtained results (Particles/mL)

	Test	≥ 2 µm	≥ 10 µm	≥ 25 µm
Day 1	1	63	0	0
	2	444	32	0
	3	190	32	0
	4	0	0	0
	5	32	0	0
	6	32	0	0
	7	95	0	0
	8	63	0	0
	9	32	0	0
	10	127	0	0
	11	32	0	0
	12	63	0	0
	13	730	0	0
	14	95	0	0
	15	317	0	0
	16	254	0	0
	17	127	0	0
	18	222	0	0
	19	159	32	0
	20	95	32	0
Day 2	21	508	32	0
	22	95	32	0
	23	222	95	63
	24	476	0	0
	25	254	32	0
	26	444	0	0
	27	190	0	0
	28	222	32	0
	29	222	0	0
	30	159	0	0
Day 3	31	32	0	0
	32	32	0	0
	33	95	0	0

	34	0	0	0
	35	317	0	0
	36	127	0	0
	37	159	63	0
	38	222	0	0
	39	540	127	95
	40	95	0	0
	41	127	0	0
	42	254	63	0
	43	190	0	0
	44	190	32	32
	45	127	0	0
	46	159	63	0
	47	444	63	0
	48	381	0	0
	49	222	32	0
	50	381	95	0

HIAC

Table A.2: HIAC obtained results (Particles/mL)

	Test	≥ 2 µm	≥ 10 µm	≥ 25 µm
Day 1	1	43.33	6.67	0
	2	130	11.67	0
	3	108.33	1.67	0
	4	21.67	3.33	1.67
	5	31.67	1.67	0
	6	83.33	8.33	0
	7	21.67	5	0
	8	78.33	11.67	0
	9	106.67	5	0
	10	126.67	6.67	1.67
Day 2	11	135	11.67	0
	12	143	20	1.67
	13	170	11.67	0
	14	76.67	3.33	0
	15	116.67	6.67	0
	16	218.33	25	10
	17	275	28.33	0
	18	361.67	21.67	0
	19	416.67	10	1.67
	20	550	25	3.33
Day 3	21	76.67	3.33	0
	12	75	1.67	0
	23	130	16.67	3.33
	24	81.67	8.33	0
	25	86.67	1.67	0
	26	161.67	10	1.67
	27	75	16.67	5
	28	111.67	16.67	0
	29	378.33	30	0
	30	166.67	8.33	1.67

A2. Study in PFS results

pH

Table A.3: pH measured values

pH measurements		Agitation	T0	T1w	T2w	T3w	T4w	T5w
5°C	F1 _1			6.985	7.013	7.050	7.012	6.940
	F1 _2			6.978	6.965	7.042	6.950	6.947
	F2 _1			6.955	6.991	7.018	6.984	6.938
	F2 _2			6.953	7.011	7.033	6.935	6.936
	F3 _1			5.053	5.010	5.030	5.036	5.068
	F3 _2			5.001	5.041	5.027	5.042	5.011
	F4 _1			5.020	5.074	5.001	5.046	5.047
	F4 _2			5.028	5.053	4.991	4.992	4.998
	F5 _1			4.995	4.967	5.006	5.022	5.016
	F5 _2			4.988	4.953	4.998	4.982	4.979
25°C	F1 _1	7.030	7.078	6.952	6.985	6.997	6.957	6.95
	F1 _2	/	/	6.956	6.998	6.994	6.952	6.955
	F2 _1	7.038	7.057	6.935	6.981	6.992	6.953	6.937
	F2 _2	/	/	6.932	6.979	6.996	6.922	6.935
	F3 _1	5.011	5.028	5.057	5.063	5.036	5.063	5.088
	F3 _2	/	/	5.022	5.022	5.024	5.006	5.037
	F4 _1	5.003	5.02	5.013	5.051	5.032	5.037	5.015
	F4 _2	/	/	5.011	5.031	5.037	4.961	4.987
	F5 _1	4.991	5.019	4.992	5.024	5.002	5.038	5.017
	F5 _2	/	/	4.979	5.005	5.003	4.969	4.998

Table A.4: pH averages

pH averages		Agitation	T0	T1w	T2w	T3w	T4w	T5w
5°C	F1 / 5°C			6.982	6.989	7.046	6.981	6.944
	F2 / 5°C			6.954	7.001	7.026	6.960	6.937
	F3 / 5°C			5.027	5.026	5.029	5.039	5.040
	F4 / 5°C			5.024	5.064	4.996	5.019	5.023
	F5 / 5°C			4.992	4.960	5.002	5.002	4.998
25°C	F1 / 25°C	7.030	7.078	6.954	6.992	6.996	6.955	6.953
	F2 / 25°C	7.038	7.057	6.934	6.980	6.994	6.938	6.936
	F3 / 25°C	5.011	5.028	5.040	5.043	5.030	5.035	5.063
	F4 / 25°C	5.003	5.020	5.012	5.041	5.035	4.999	5.001
	F5 / 25°C	4.991	5.019	4.986	5.015	5.003	5.004	5.008

Osmolarity

Table A.5: Osmolarity measured values

Osmolarity measurement		Agitation	T0	T1w	T2w	T3w	T4w	T5w
5°C	F1 _1			0.415	0.403	0.406	0.401	0.405
	F1 _2			0.408	0.404	0.404	0.402	0.406
	F2 _1			0.412	0.407	0.404	0.403	0.412
	F2 _2			0.413	0.416	0.404	0.398	0.411
	F3 _1			0.279	0.276	0.279	0.272	0.275
	F3 _2			0.274	0.278	0.276	0.275	0.280
	F4 _1			0.308	0.296	0.296	0.295	0.296
	F4 _2			0.292	0.300	0.296	0.291	0.295
	F5 _1			0.276	0.277	0.277	0.270	0.275
	F5 _2			0.286	0.291	0.278	0.277	0.279
25°C	F1 _1	0.413	0.392	0.415	0.400	0.409	0.399	0.408
	F1 _2	0.408	0.433	0.408	0.416	0.402	0.398	0.407
	F2 _1	0.416	0.398	0.416	0.405	0.41	0.401	0.408
	F2 _2	0.406	0.407	0.418	0.408	0.41	0.399	0.417
	F3 _1	0.279	0.273	0.284	0.276	0.275	0.276	0.275
	F3 _2	0.280	0.279	0.284	0.28	0.283	0.277	0.275
	F4 _1	0.299	0.273	0.294	0.297	0.301	0.292	0.298
	F4 _2	0.300	0.299	0.298	0.288	0.303	0.294	0.296
	F5 _1	0.262	0.267	0.276	0.273	0.278	0.269	0.282
	F5 _2	0.276	0.276	0.28	0.281	0.28	0.269	0.282

Table A.6: Osmolarity averages

Osmolarity averages		Agitation	T0	T1w	T2w	T3w	T4w	T5w
5°C	F1 / 5°C	0.411	0.413	0.412	0.404	0.405	0.402	0.406
	F2 / 5°C	0.411	0.403	0.413	0.412	0.404	0.401	0.412
	F3 / 5°C	0.280	0.276	0.277	0.277	0.278	0.274	0.278
	F4 / 5°C	0.300	0.286	0.300	0.298	0.296	0.293	0.296
	F5 / 5°C	0.269	0.272	0.281	0.284	0.278	0.274	0.277
25°C	F1 / 25°C	0.411	0.413	0.412	0.408	0.406	0.399	0.408
	F2 / 25°C	0.411	0.403	0.417	0.407	0.410	0.400	0.413
	F3 / 25°C	0.280	0.276	0.284	0.278	0.279	0.277	0.275
	F4 / 25°C	0.300	0.286	0.296	0.293	0.302	0.293	0.297
	F5 / 25°C	0.269	0.272	0.278	0.277	0.279	0.269	0.282

HORIZON VUE

Table A.7: HORIZON VUE obtained results (Particles/mL)

		≥2µm	≥10 µm	≥25 µm			≥2µm	≥10 µm	≥25 µm
T0	**F1**	286	32	32	**Agitació**	**F1**	698	0	0
		317	32	32			540	32	0
		444	32	0			2095	127	0
		222	63	32			1556	127	0
		349	32	32			1175	95	32
	F2	159	0	0		**F2**	444	32	32
		730	222	159			444	63	32
		63	32	32			381	0	0
		476	95	32			857	32	0
		63	0	0			571	32	0
	F3	317	0	0		**F3**	444	0	0
		635	222	63			190	0	0
		762	159	63			190	63	32
		413	127	63			190	63	0
		413	32	32			286	0	0
	F4	317	32	32		**F4**	1079	32	0
		444	95	32			476	32	32
		222	32	32			476	32	0
		254	0	0			444	0	0
		63	0	0			3524	0	0
	F5	1270	254	63		**F5**	127	0	0
		317	159	127			222	32	0
		698	222	32			349	0	0
		603	95	95			95	0	0
		349	127	32			127	0	0
T1 5°C	**F1**	540	32	0	**T1 25°C**	**F1**	794	159	127
		381	0	0			476	32	0
		349	0	0			317	0	0
	F2	286	32	0		**F2**	698	32	0
		190	32	0			540	0	0
		159	0	0			508	0	0
	F3	349	32	0		**F3**	1524	0	0
		254	32	0			1460	0	0
		222	0	0			571	32	0
	F4	540	32	0		**F4**	413	0	0
		540	63	0			286	32	32
		63	0	0			254	0	0
	F5	349	32	0		**F5**	444	32	0

		222	0	0			317	0	0
		222	0	0			222	0	0
T2 5°C	**F1**	476	63	0	**T2 25°C**	**F1**	603	0	0
		381	32	0			444	0	0
		381	32	32			413	0	0
	F2	476	0	0		**F2**	857	190	0
		444	32	0			730	63	32
		349	32	0			603	95	63
	F3	1143	63	0		**F3**	667	0	0
		1016	0	0			571	95	32
		444	0	0			571	0	0
	F4	762	0	0		**F4**	476	95	63
		571	63	0			444	0	0
		349	32	0			381	63	32
	F5	762	0	0		**F5**	444	32	0
		254	32	32			381	0	0
		190	0	0			286	0	0
T3 5°C	**F1**	698	95	0	**T3 25°C**	**F1**	889	32	0
		381	63	0			857	32	0
		127	0	0			730	32	0
		95	0	0			508	32	32
		0	0	0			444	32	0
	F2	2349	95	0		**F2**	730	63	0
		1429	95	0			603	95	0
		1333	63	32			508	0	0
		1333	63	32			444	0	0
		857	63	0			349	0	0
	F3	667	32	0		**F3**	1365	127	0
		571	32	0			1206	222	32
		222	0	0			1016	127	63
		698	32	0			730	0	0
		444	32	0			635	127	0
	F4	540	0	0		**F4**	952	32	0
		444	32	0			952	32	32
		317	0	0			794	0	0
							762	0	0
							1968	32	0
	F5	476	63	32		**F5**	889	32	32
		476	32	32			857	32	0
		349	32	0			667	32	32
T4 5°C	**F1**	317	63	32	**T4 25°C**	**F1**	540	63	0
		190	0	0			444	0	0

		63	0	0			349	0	0
		63	0	0			317	32	0
		32	32	0			286	0	0
	F2	254	0	0		**F2**	349	63	0
		127	0	0			127	0	0
		32	0	0			63	0	0
		32	0	0			32	0	0
		32	0	0			0	0	0
	F3	825	0	0		**F3**	794	0	0
		381	32	32			349	32	0
		222	0	0			317	32	0
		190	0	0			159	32	0
		63	0	0			127	0	0
	F4	317	63	0		**F4**	667	0	0
		222	0	0			571	0	0
		127	0	0			159	0	0
		63	0	0			127	0	0
		32	0	0			254	32	0
	F5	254	0	0		**F5**	254	0	0
		95	0	0			159	32	0
		63	0	0			127	0	0
		32	0	0			127	0	0
		0	0	0			63	32	0
T5 5°C	**F1**	603	0	0	**T5 25°C**	**F1**	540	95	0
		571	32	0			540	63	32
		540	0	0			476	0	0
		254	0	0			381	32	0
		95	32	32			317	32	0
	F2	159	0	0		**F2**	127	0	0
		127	0	0			127	0	0
		95	0	0			127	63	0
		63	0	0			95	0	0
		0	0	0			32	0	0
	F3	476	0	0		**F3**	730	0	0
		254	32	32			508	0	0
		222	0	0			349	0	0
		190	32	0			254	32	0
		95	0	0			222	0	0
	F4	159	32	32		F4	698	0	0
		159	32	32			127	32	0
		95	0	0			127	32	0
		95	0	0			63	0	0

		63	0	0			32	0	0
	F5	349	0	0		F5	159	63	0
		254	0	0			159	32	0
		159	32	0			127	0	0
		127	0	0			63	0	0
		95	0	0			32	0	0

HIAC

Table A.8: HIAC obtained results (Particles/mL)

		>2 µm	>10 µm	>25µm			>2 µm	>10 µm	>25µm
T0	**F1**	226.67	13.33	3.33	**T0**	**F1**	916.67	45	3.33
		201.67	8.33	0			876.67	33.33	0
	F2	140	3.33	0		**F2**	93.33	5	0
		146.67	15	0			93.33	3.33	0
	F3	126.67	5	1.67		**F3**	278.33	11.67	0
		160	10	0			313.33	5	1.67
	F4	128.33	8.33	0		**F4**	121.67	13.33	3.33
		118.33	6.67	0			121.67	10	1.67
	F5	110	6.67	0		**F5**	65	5	0
		128.33	5	0			25	0	0
T1 5°C	**F1**	248.33	8.33	0	**T1 25°C**	**F1**	508.33	18.33	0
		265	16.67	5			560	15	0
	F2	98.33	5	1.67		**F2**	480	11.67	0
		150	8.33	1.67			591.67	6.67	0
	F3	158.33	13.33	0		**F3**	1068	51.67	0
		146.67	15	1.67			1258.33	93.33	1.67
	F4	120	8.33	1.67		**F4**	-	-	-
		138.33	6.67	3.33			668.33	45	0
	F5	55	11.67	0		**F5**	-	-	-
		83.33	13.33	1.67			305	41.67	1.67
T2 5°C	**F1**	235	3.33	0	**T2 25°C**	**F1**	426.67	6.67	0
		255	5	0			508.33	13.33	0
	F2	93.33	6.67	0		**F2**	700	11.67	0
		120	5	0			760	3.33	0
	F3					**F3**	511.67	28.33	0
		141.67	5	0			683.33	18.33	0
	F4	135	5	1.67		**F4**	546.67	15	0
		156.67	5	1.67			826.67	41.67	0
	F5	80	3.33	0		**F5**	158.33	13.33	0

		115	10	0			205	11.67	0
T3 5°C	**F1**	281.67	8.33	1.67	**T3 25°C**	**F1**	1205	48.33	1.67
		258.33	16.67	0			971.67	30	0
	F2	505	8.33	0		**F2**	60	0	0
		488.33	10	0			88.33	0	0
	F3	105	6.67	0		**F3**	233.33	8.33	0
		110	6.67	0			315	21.67	0
	F4	553.33	23.33	0		**F4**	813.33	30	0
		593.33	36.67	1.67			968.33	53.33	1.67
	F5	53.33	3.33	0		**F5**	238.33	11.67	0
		78.33	6.667	0			130	6.67	0
T4 5°C	**F1**	206.67	6.67	0	**T4 25°C**	**F1**	273.33	3.33	0
		220	6.67	0			295	8.33	0
	F2	58.33	5	0		**F2**	100	5	0
		98.33	8.33	0			120	8.33	1.67
	F3	363.33	15	0		**F3**	340	15	0
		423.33	15	0			391.67	23.33	0
	F4	166.67	16.67	5		**F4**	323.33	15	0
		206.67	13.33	0			386.67	23.33	1.67
	F5	35	1.67	0		**F5**	426.67	55	0
		56.67	11.67	0			521.67	140	0
T5 5°C	**F1**	213.33	25	0	**T5 25°C**	**F1**	598.33	20	0
		198.33	23.33	0			660	25	0
	F2	115	0	0		**F2**	250	3.33	1.67
		148.33	1.67	0			253.33	3.33	0
	F3	510	31.67	1.67		**F3**	430	20	0
		335	25	0			403.33	20	3.33
	F4	80	5	0		**F4**	801.67	43.33	1.67
		131.67	3.33	0			916.67	40	0
	F5	111.67	26.67	3.33		**F5**	136.67	8.33	0
		96.67	21.67	0			133.33	5	0

Annex B: Safety data sheets

All the Safety data sheets are obtained from Merck's webpage [13].

Acetic acid

Supelco®

www.sigmaaldrich.com

SAFETY DATA SHEET
according to Regulation (EC) No. 1907/2006

Version 6.8
Revision Date 04.06.2021
Print Date 05.05.2022
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : Acetic acid (glacial) 100% anhydrous for analysis EMSURE® ACS,ISO,Reag. Ph Eur

Product Number	:	1.00063
Catalogue No.	:	100063
Brand	:	Millipore
Index-No.	:	607-002-00-6
REACH No.	:	01-2119475328-30-XXXX
CAS-No.	:	64-19-7

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Reagent for analysis, Chemical production

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich Chemie GmbH
Eschenstrasse 5
D-82024 TAUFKIRCHEN

Telephone	:	+49 (0)89 6513-1130
Fax	:	+49 (0)89 6513-1161
E-mail address	:	technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone # : 0800 181 7059 (CHEMTREC Deutschland)
+49 (0)696 43508409 (CHEMTREC weltweit)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Classification according to Regulation (EC) No 1272/2008
Flammable liquids (Category 3), H226
Skin corrosion (Sub-category 1A), H314
Serious eye damage (Category 1), H318

For the full text of the H-Statements mentioned in this Section, see Section 16.

2.2 Label elements

Labelling according Regulation (EC) No 1272/2008

Millipore- 1.00063

Page 1 of 11

The life science business of Merck operates as MilliporeSigma in the US and Canada

Pictogram	
Signal word	Danger
Hazard statement(s)	
H226	Flammable liquid and vapor.
H314	Causes severe skin burns and eye damage.
Precautionary statement(s)	
P210	Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking.
P233	Keep container tightly closed.
P240	Ground and bond container and receiving equipment.
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection.
P303 + P361 + P353	IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water.
P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
Supplemental Hazard Statements	none

Reduced Labeling (<= 125 ml)

Pictogram	
Signal word	Danger
Hazard statement(s)	
H314	Causes severe skin burns and eye damage.
Precautionary statement(s)	
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection.
P303 + P361 + P353	IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water.
P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
Supplemental Hazard Statements	none

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

Formula	:	C2H4O2
Molecular weight	:	60,05 g/mol
CAS-No.	:	64-19-7
EC-No.	:	200-580-7

Index-No. : 607-002-00-6

Component		Classification	Concentration
acetic acid			
CAS-No. EC-No. Index-No.	64-19-7 200-580-7 607-002-00-6	Flam. Liq. 3; Skin Corr. 1A; Eye Dam. 1; H226, H314, H318 Concentration limits: >= 90 %: Skin Corr. 1A, H314; 25 - < 90 %: Skin Corr. 1B, H314; 10 - < 25 %: Skin Irrit. 2, H315; 10 - < 25 %: Eye Irrit. 2, H319; 10 - < 25 %: Eye Irrit. 2, H319; 10 - < 25 %: Skin Irrit. 2, H315; 25 - < 90 %: Skin Corr. 1B, H314; >= 90 %: Skin Corr. 1A, H314; >= 90 %: 3, H226;	<= 100 %

For the full text of the H-Statements mentioned in this Section, see Section 16.

SECTION 4: First aid measures

4.1 Description of first-aid measures

General advice
First aiders need to protect themselves. Show this material safety data sheet to the doctor in attendance.

If inhaled
After inhalation: fresh air. Call in physician.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower. Call a physician immediately.

In case of eye contact
After eye contact: rinse out with plenty of water. Immediately call in ophthalmologist. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most), avoid vomiting (risk of perforation). Call a physician immediately. Do not attempt to neutralise.

4.2 Most important symptoms and effects, both acute and delayed

The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed

No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Water Foam Carbon dioxide (CO2) Dry powder

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture

Carbon oxides
Combustible.
Fire may cause evolution of:
Acetic acid vapours
Vapors are heavier than air and may spread along floors.
Forms explosive mixtures with air at elevated temperatures.
Development of hazardous combustion gases or vapours possible in the event of fire.

5.3 Advice for firefighters

Stay in danger area only with self-contained breathing apparatus. Prevent skin contact by keeping a safe distance or by wearing suitable protective clothing.

5.4 Further information

Remove container from danger zone and cool with water. Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

Advice for non-emergency personnel: Do not breathe vapors, aerosols. Avoid substance contact. Ensure adequate ventilation. Keep away from heat and sources of ignition.
Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions

Do not let product enter drains. Risk of explosion.

6.3 Methods and materials for containment and cleaning up

Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up with liquid-absorbent and neutralising material (e.g. Chemizorb® H^+, Merck Art. No. 101595). Dispose of properly. Clean up affected area.

6.4 Reference to other sections

For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Advice on protection against fire and explosion
Keep away from open flames, hot surfaces and sources of ignition.Take precautionary measures against static discharge.

Hygiene measures
Immediately change contaminated clothing. Apply preventive skin protection. Wash hands and face after working with substance.
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Keep container tightly closed in a dry and well-ventilated place. Keep away from heat and sources of ignition.

Recommended storage temperature see product label.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Tightly fitting safety goggles

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Full contact
Material: butyl-rubber
Minimum layer thickness: 0,7 mm
Break through time: 480 min
Material tested:Butoject® (KCL 898)

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Latex gloves
Minimum layer thickness: 0,6 mm
Break through time: 30 min
Material tested:Lapren® (KCL 706 / Aldrich Z677558, Size M)

Body Protection
Flame retardant antistatic protective clothing.

Respiratory protection
Recommended Filter type: filter E-(P2)

The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure
Do not let product enter drains. Risk of explosion.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: liquid Color: colorless
b)	Odor	stinging
c)	Odor Threshold	0,2 ppm
d)	pH	2,5 at 50 g/l at 20 °C
e)	Melting point/freezing point	Melting point: 16,64 °C
f)	Initial boiling point and boiling range	117,9 °C at 1.013,25 hPa
g)	Flash point	39 °C - closed cup
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	Not applicable
j)	Upper/lower flammability or explosive limits	Upper explosion limit: 19,9 %(V) Lower explosion limit: 4 %(V)
k)	Vapor pressure	20,79 hPa at 25 °C
l)	Vapor density	2,07
m)	Relative density	No data available
n)	Water solubility	602,9 g/l at 25 °C at 1.013 hPa - completely soluble
o)	Partition coefficient: n-octanol/water	log Pow: -0,17 at 25 °C - Bioaccumulation is not expected., (ECHA)
p)	Autoignition temperature	463 °C
q)	Decomposition temperature	Distillable in an undecomposed state at normal pressure.
r)	Viscosity	Viscosity, kinematic: 1,17 mm2/s at 20 °C Viscosity, dynamic: 1,05 mPa.s at 25 °C
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information

Surface tension	28,8 mN/m at 10,0 °C

Relative vapor density	2,07

SECTION 10: Stability and reactivity

10.1 Reactivity
Vapor/air-mixtures are explosive at intense warming.

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
No data available

10.4 Conditions to avoid
Heating.

10.5 Incompatible materials
various metals

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - 3.310 mg/kg
Remarks: (RTECS)
LC50 Inhalation - Mouse - 4 h - 2.819 mg/l
Remarks: (RTECS)
Dermal: No data available

Skin corrosion/irritation
Skin - Rabbit
Result: Causes burns. - 4 h
(OECD Test Guideline 404)
Remarks: (IUCLID)

Serious eye damage/eye irritation
Eyes - Rabbit
Result: Causes burns. - 4 h
(OECD Test Guideline 405)
Remarks: (IUCLID)
Causes serious eye damage.

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
Test Type: Ames test
Test system: Salmonella typhimurium
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 471
Result: negative
Test Type: Mutagenicity (mammal cell test): chromosome aberration.

Test system: Chinese hamster ovary cells
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 473
Result: negative

Test Type: Micronucleus test
Species: Rat
Cell type: Bone marrow
Application Route: inhalation (vapor)
Method: Mutagenicity (micronucleus test)
Result: negative

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

Material is extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes, and skin., spasm, inflammation and edema of the larynx, spasm, inflammation and edema of the bronchi, pneumonitis, pulmonary edema, burning sensation, Cough, wheezing, laryngitis, Shortness of breath, Headache, Nausea, Vomiting, Ingestion or inhalation of concentrated acetic acid causes damage to tissues of the respiratory and digestive tracts. Symptoms include: hematemesis, bloody diarrhea, edema and/or perforation of the esophagus and pylorus, pancreatitis, hematuria, anuria, uremia, albuminuria, hemolysis, convulsions, bronchitis, pulmonary edema, pneumonia, cardiovascular collapse, shock, and death. Direct contact or exposure to high concentrations of vapor with skin or eyes can cause: erythema, blisters, tissue destruction with slow healing, skin blackening, hyperkeratosis, fissures, corneal erosion, opacification, iritis, conjunctivitis, and possible blindness.
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

SECTION 12: Ecological information

12.1 Toxicity

Toxicity to fish	semi-static test LC50 - Oncorhynchus mykiss (rainbow trout) - > 1.000 mg/l - 96 h (OECD Test Guideline 203)
Toxicity to daphnia and other aquatic invertebrates	static test EC50 - Daphnia magna (Water flea) - > 1.000 mg/l - 48 h (OECD Test Guideline 202)
Toxicity to algae	static test EC50 - Skeletonema costatum - > 1.000 mg/l - 72 h (ISO 10253)

Toxicity to bacteria	EC5 - Pseudomonas putida - 2.850 mg/l - 16 h Remarks: neutral (maximum permissible toxic concentration) (Lit.)
	microtox test EC50 - Photobacterium phosphoreum - 11 mg/l - 15 min Remarks: (IUCLID)

12.2 Persistence and degradability

Biodegradability	Result: 99 % - Readily biodegradable. (OECD Test Guideline 301D) Remarks: (HSDB)
	Result: 95 % - Readily eliminated from water (OECD Test Guideline 302B)
Biochemical Oxygen Demand (BOD)	880 mg/g Remarks: (Lit.)
Ratio BOD/ThBOD	76 % Remarks: (IUCLID)

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Other adverse effects
Biological effects:
Harmful effect due to pH shift. Caustic even in diluted form.
Discharge into the environment must be avoided.

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number
ADR/RID: 2789 IMDG: 2789 IATA: 2789

14.2 UN proper shipping name
ADR/RID: ACETIC ACID, GLACIAL
IMDG: ACETIC ACID, GLACIAL

IATA: Acetic acid, glacial

14.3 Transport hazard class(es)

ADR/RID: 8 (3)	IMDG: 8 (3)	IATA: 8 (3)

14.4 Packaging group

ADR/RID: II	IMDG: II	IATA: II

14.5 Environmental hazards

ADR/RID: no	IMDG Marine pollutant: no	IATA: no

14.6 Special precautions for user
No data available

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture
This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

National legislation
Seveso III: Directive 2012/18/EU of the European Parliament and of the Council on the control of major-accident hazards involving dangerous substances. : FLAMMABLE LIQUIDS

Other regulations
Take note of Dir 94/33/EC on the protection of young people at work.

15.2 Chemical Safety Assessment
A Chemical Safety Assessment has been carried out for this substance.

SECTION 16: Other information

Full text of H-Statements referred to under sections 2 and 3.

H226	Flammable liquid and vapor.
H314	Causes severe skin burns and eye damage.
H315	Causes skin irritation.
H318	Causes serious eye damage.
H319	Causes serious eye irritation.

Further information
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

The branding on the header and/or footer of this document may temporarily not visually match the product purchased as we transition our branding. However, all of the information in the document regarding the product remains unchanged and matches the product ordered. For further information please contact mlsbranding@sial.com.

Sodium acetate trihydrate

Supelco

www.sigmaaldrich.com

SAFETY DATA SHEET
according to Regulation (EC) No. 1907/2006

Version 6.7
Revision Date 01.12.2021
Print Date 05.05.2022
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : Sodium acetate trihydrate for analysis EMSURE® ACS,ISO,Reag. Ph Eur

Product Number	:	1.06267
Catalogue No.	:	106267
Brand	:	Millipore
REACH No.	:	01-2119485123-42-XXXX
CAS-No.	:	6131-90-4

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Reagent for analysis

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich Chemie GmbH
Eschenstrasse 5
D-82024 TAUFKIRCHEN

Telephone	:	+49 (0)89 6513-1130
Fax	:	+49 (0)89 6513-1161
E-mail address	:	technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone # : 0800 181 7059 (CHEMTREC Deutschland)
+49 (0)696 43508409 (CHEMTREC weltweit)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

Formula	:	C2H3O2Na.3H2O
Molecular weight	:	136,08 g/mol
CAS-No.	:	6131-90-4
EC-No.	:	204-823-8

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first-aid measures

If inhaled
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Water Foam Carbon dioxide (CO2) Dry powder

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Nature of decomposition products not known.
Combustible.
Development of hazardous combustion gases or vapours possible in the event of fire.

5.3 Advice for firefighters
In the event of fire, wear self-contained breathing apparatus.

5.4 Further information
Suppress (knock down) gases/vapors/mists with a water spray jet. Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Avoid inhalation of dusts. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up dry. Dispose of properly. Clean up affected area. Avoid generation of dusts.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed. Dry.

Recommended storage temperature see product label.

Storage class
Storage class (TRGS 510): 11: Combustible Solids

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Full contact
Material: Nitrile rubber

Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Respiratory protection
required when dusts are generated.
Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.
Recommended Filter type: Filter type P1

The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: solid Color: colorless
b)	Odor	No data available
c)	Odor Threshold	No data available
d)	pH	8,5 - 10 at 408 g/l at 25 °C
e)	Melting point/freezing point	Melting point/range: 57,9 °C
f)	Initial boiling point and boiling range	No data available
g)	Flash point	No data available
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	No data available
k)	Vapor pressure	No data available

l)	Vapor density	No data available
m)	Density	1,45 g/cm3
	Relative density	No data available
n)	Water solubility	408 g/l at 20 °C - completely soluble
o)	Partition coefficient: n-octanol/water	No data available
p)	Autoignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	none

9.2 Other safety information

Bulk density	ca.900 kg/m3

SECTION 10: Stability and reactivity

10.1 Reactivity
The following applies in general to flammable organic substances and mixtures: in correspondingly fine distribution, when whirled up a dust explosion potential may generally be assumed.

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
No data available

10.4 Conditions to avoid
no information available

10.5 Incompatible materials
Strong oxidizing agents

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - 3.530 mg/kg
Remarks: (anhydrous substance)
(RTECS)
The value is given in analogy to the following substances: sodium acetate
LC50 Inhalation - Rat - male and female - 4 h - > 5,6 mg/l - dust/mist

(OECD Test Guideline 403)
Remarks: (anhydrous substance)
The value is given in analogy to the following substances: sodium acetate
LD50 Dermal - Rabbit - female - > 20.000 mg/kg
(OECD Test Guideline 402)
Remarks: (anhydrous substance)
The value is given in analogy to the following substances: sodium acetate

Skin corrosion/irritation
Skin - Rabbit
Result: No irritation - 72 h
(OECD Test Guideline 404)
Remarks: (anhydrous substance)
The value is given in analogy to the following substances: sodium acetate

Serious eye damage/eye irritation
Eyes - Rabbit
Result: No eye irritation - 72 h
(OECD Test Guideline 405)
Remarks: (anhydrous substance)
The value is given in analogy to the following substances: sodium acetate

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

SECTION 12: Ecological information

12.1 Toxicity

Toxicity to fish	semi-static test LC50 - Danio rerio (zebra fish) - > 100 mg/l - 96 h (OECD Test Guideline 203) Remarks: (anhydrous substance) The value is given in analogy to the following substances: sodium acetate

Toxicity to daphnia and other aquatic invertebrates	static test EC50 - Daphnia magna Straus (Water flea) - > 919 mg/l - 48 h (OECD Test Guideline 202) Remarks: (anhydrous substance) The value is given in analogy to the following substances: sodium acetate
Toxicity to algae	ErC50 - Skeletonema costatum - > 1.000 mg/l - 72 h (ISO 10253) Remarks: (anhydrous substance) The value is given in analogy to the following substances: sodium acetate
Toxicity to bacteria	static test EC50 - Pseudomonas putida - 7.200 mg/l - 16 h (DIN 38421 TEIL 8) Remarks: (anhydrous substance) The value is given in analogy to the following substances: sodium acetate

12.2 Persistence and degradability

Biodegradability	aerobic - Exposure time 28 d Result: 99 % - Readily biodegradable. (OECD Test Guideline 301A) Remarks: (anhydrous substance)

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Endocrine disrupting properties
No data available

12.7 Other adverse effects
Discharge into the environment must be avoided.

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number
ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name
ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)
ADR/RID: - IMDG: - IATA: -

14.4 Packaging group
ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards
ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

Further information
Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture
This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

15.2 Chemical Safety Assessment
For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Further information
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

The branding on the header and/or footer of this document may temporarily not visually match the product purchased as we transition our branding. However, all of the information in the document regarding the product remains unchanged and matches the product ordered. For further information please contact mlsbranding@sial.com.

Sodium dihydrogen phosphate monohydrate

Supelco®

www.sigmaaldrich.com

SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 6.2
Revision Date 27.03.2021
Print Date 05.05.2022
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : Sodium dihydrogen phosphate monohydrate for analysis EMSURE® ACS,Reag. Ph Eur

Product Number : 1.06346
Catalogue No. : 106346
Brand : Millipore
REACH No. : 01-2119489796-13-XXXX
CAS-No. : 10049-21-5

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Reagent for analysis

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich Chemie GmbH
Eschenstrasse 5
D-82024 TAUFKIRCHEN

Telephone : +49 (0)89 6513-1130
Fax : +49 (0)89 6513-1161
E-mail address : technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone # : 0800 181 7059 (CHEMTREC Deutschland)
+49 (0)696 43508409 (CHEMTREC weltweit)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

Formula	:	$NaH_2PO_4 \cdot H_2O$
Molecular weight	:	137,99 g/mol
CAS-No.	:	10049-21-5
EC-No.	:	231-449-2

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first-aid measures

If inhaled
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Oxides of phosphorus
Sodium oxides
Not combustible.
Fire may cause evolution of:
Oxides of phosphorus
Ambient fire may liberate hazardous vapours.

5.3 Advice for firefighters
In the event of fire, wear self-contained breathing apparatus.

5.4 Further information
Suppress (knock down) gases/vapors/mists with a water spray jet. Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Avoid inhalation of dusts. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up dry. Dispose of properly. Clean up affected area. Avoid generation of dusts.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed. Dry.

Recommended storage temperature see product label.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Respiratory protection
required when dusts are generated.
Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.
Recommended Filter type: Filter type P1

The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: crystals Color: colorless
b)	Odor	No data available
c)	Odor Threshold	No data available
d)	pH	4,1 - 4,5 at 50 g/l at 25 °C
e)	Melting point/freezing point	Melting point: 100 °C
f)	Initial boiling point and boiling range	No data available
g)	Flash point	Not applicable
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	The product is not flammable.
j)	Upper/lower flammability or	No data available

	explosive limits	
k)	Vapor pressure	No data available
l)	Vapor density	No data available
m)	Relative density	No data available
n)	Water solubility	at 20 °C soluble
o)	Partition coefficient: n-octanol/water	Not applicable for inorganic substances
p)	Autoignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information

Bulk density ca.880 kg/m3

SECTION 10: Stability and reactivity

10.1 Reactivity
No data available

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
Violent reactions possible with:
Strong acids

10.4 Conditions to avoid
no information available

10.5 Incompatible materials
Strong oxidizing agents

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - > 2.000 mg/kg
(OECD Test Guideline 401)
Remarks: (in analogy to similar products)The value is given in analogy to the following substances: sodium dihydrogen phosphate

LC50 Inhalation - Rat - male and female - 4 h - > 0,83 mg/l
(OECD Test Guideline 403)
Remarks: (in analogy to similar products)The value is given in analogy to the following substances: sodium dihydrogen phosphate

LD50 Dermal - Rabbit - > 7.940 mg/kg
Remarks: (anhydrous substance)
(IUCLID)

Skin corrosion/irritation
Skin - Rabbit
Result: No skin irritation - 4 h
(OECD Test Guideline 404)
Remarks: (in analogy to similar products)

Serious eye damage/eye irritation
Eyes - Rabbit
Result: slight irritation
Remarks: (IUCLID)

Respiratory or skin sensitization
Sensitisation test: - Mouse
(OECD Test Guideline 429)

Germ cell mutagenicity
No data available

Test Type: Mutagenicity (mammal cell test): micronucleus.
Test system: Human lymphocytes
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 487
Result: negative

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information
Not available

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

Handle in accordance with good industrial hygiene and safety practice.

SECTION 12: Ecological information

12.1 Toxicity

Toxicity to fish	LC0 - Leuciscus idus (Golden orfe) - ca. 2.400 mg/l - 48 h (OECD Test Guideline 203) Remarks: (anhydrous substance)

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Other adverse effects
No data available
Discharge into the environment must be avoided.
Depending on the concentration, phosphates may contribute to the eutrophication of water supplies.

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number
ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name
ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)
ADR/RID: - IMDG: - IATA: -

14.4 Packaging group
ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards
ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

Further information
Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture
This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

National legislation
Seveso III: Directive 2012/18/EU of the European Parliament and of the Council on the control of major-accident hazards involving dangerous substances. : Not applicable

15.2 Chemical Safety Assessment
For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Further information
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

The branding on the header and/or footer of this document may temporarily not visually match the product purchased as we transition our branding. However, all of the information in the document regarding the product remains unchanged and matches the product ordered. For further information please contact mlsbranding@sial.com.

Di-Sodium hydrogen phosphate heptahydrate

SAFC®

www.sigmaaldrich.com

SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 8.4
Revision Date 04.06.2021
Print Date 05.05.2022
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : di-Sodium hydrogen phosphate heptahydrate
EMPROVE® ESSENTIAL DAC,USP

Product Number : 1.06574
Catalogue No. : 106574
Brand : Millipore
REACH No. : 01-2119489797-11-XXXX
CAS-No. : 7782-85-6

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Pharmaceutical production, Cosmetic raw material

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich Chemie GmbH
Eschenstrasse 5
D-82024 TAUFKIRCHEN

Telephone : +49 (0)89 6513-1130
Fax : +49 (0)89 6513-1161
E-mail address : technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone # : 0800 181 7059 (CHEMTREC Deutschland)
+49 (0)696 43508409 (CHEMTREC weltweit)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

Formula	:	Na2HPO4 · 7H2O
Molecular weight	:	268,07 g/mol
CAS-No.	:	7782-85-6
EC-No.	:	237-707-0

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first-aid measures

If inhaled
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Oxides of phosphorus
Sodium oxides
Not combustible.
Fire may cause evolution of:
Oxides of phosphorus
Ambient fire may liberate hazardous vapours.

5.3 Advice for firefighters
In the event of fire, wear self-contained breathing apparatus.

5.4 Further information
Suppress (knock down) gases/vapors/mists with a water spray jet. Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Avoid inhalation of dusts. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up dry. Dispose of properly. Clean up affected area. Avoid generation of dusts.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed. Dry.

Recommended storage temperature see product label.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Respiratory protection
required when dusts are generated.
Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.
Recommended Filter type: Filter type P1

The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: solid Color: white
b)	Odor	No data available
c)	Odor Threshold	No data available
d)	pH	9,0 - 9,3 at 50 g/l at 25 °C
e)	Melting point/freezing point	No data available
f)	Initial boiling point and boiling range	No data available
g)	Flash point	Not applicable
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	The product is not flammable.
j)	Upper/lower flammability or	No data available

	explosive limits	
k)	Vapor pressure	No data available
l)	Vapor density	No data available
m)	Relative density	1,68
n)	Water solubility	No data available
o)	Partition coefficient: n-octanol/water	No data available
p)	Autoignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information

Bulk density ca.800 kg/m3

SECTION 10: Stability and reactivity

10.1 Reactivity
No data available

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
Exothermic reaction with:
Strong acids
antipyrine
Lead
acetates

10.4 Conditions to avoid
no information available

10.5 Incompatible materials
No data available

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - 12.930 mg/kg
Remarks: (RTECS)
Inhalation: No data available

Dermal: No data available

Skin corrosion/irritation
Skin - Rabbit
Result: Mild skin irritation
(OECD Test Guideline 404)
Remarks: (External MSDS)

Serious eye damage/eye irritation
Eyes - Rabbit
Result: Mild eye irritation
(OECD Test Guideline 405)
Remarks: (External MSDS)

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
Test Type: Ames test
Result: negative
Remarks: (anhydrous substance)
(National Toxicology Program)

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

Handle in accordance with good industrial hygiene and safety practice.

SECTION 12: Ecological information

12.1 Toxicity

Toxicity to daphnia and other aquatic invertebrates	EC50 - Daphnia magna (Water flea) - 1.089 mg/l - 48 h Remarks: (anhydrous substance) (Lit.)

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Other adverse effects
No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number
ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name
ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)
ADR/RID: - IMDG: - IATA: -

14.4 Packaging group
ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards
ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

Further information
Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture
This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

15.2 Chemical Safety Assessment
For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

The branding on the header and/or footer of this document may temporarily not visually match the product purchased as we transition our branding. However, all of the information in the document regarding the product remains unchanged and matches the product ordered. For further information please contact mlsbranding@sial.com.

Polysorbate 20

SAFC®

www.sigmaaldrich.com

SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 8.4
Revision Date 14.12.2021
Print Date 05.05.2022
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name	:	Tween® 20 (Polysorbate) EMPROVE® ESSENTIAL Ph Eur,JPE,NF
Product Number	:	8.17072
Catalogue No.	:	817072
Brand	:	Millipore
REACH No.	:	A registration number is not available for this substance as the substance or its uses are exempted from registration, the annual tonnage does not require a registration or the registration is envisaged for a later registration deadline.
CAS-No.	:	9005-64-5

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses	:	Pharmaceutical production, Chemical for synthesis, Cosmetic raw material

1.3 Details of the supplier of the safety data sheet

Company	:	Sigma-Aldrich Chemie GmbH Eschenstrasse 5 D-82024 TAUFKIRCHEN
Telephone	:	+49 (0)89 6513-1130
Fax	:	+49 (0)89 6513-1161
E-mail address	:	technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone #	:	0800 181 7059 (CHEMTREC Deutschland) +49 (0)696 43508409 (CHEMTREC weltweit)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

2.3 Other hazards
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

Formula	:	C58H114O26
Molecular weight	:	1.228 g/mol
CAS-No.	:	9005-64-5
EC-No.	:	500-018-3

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first-aid measures

If inhaled
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Water Foam Carbon dioxide (CO2) Dry powder

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Combustible.
Vapors are heavier than air and may spread along floors.
Forms explosive mixtures with air on intense heating.
Development of hazardous combustion gases or vapours possible in the event of fire.

5.3 Advice for firefighters
In the event of fire, wear self-contained breathing apparatus.

5.4 Further information
Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Do not breathe vapors, aerosols. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up with liquid-absorbent material (e.g. Chemizorb®). Dispose of properly. Clean up affected area.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed.

Recommended storage temperature see product label.

Storage class
Storage class (TRGS 510): 10: Combustible liquids

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Full contact
Material: Nitrile rubber
Minimum layer thickness: 0,4 mm
Break through time: 480 min
Material tested:Camatril® (KCL 730 / Aldrich Z677442, Size M)

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 30 min
Material tested:KCL 741 Dermatril® L

Respiratory protection
Not required; except in case of aerosol formation.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: liquid Color: yellow
b)	Odor	odorless
c)	Odor Threshold	No data available
d)	pH	7
e)	Melting point/freezing point	Melting point: 98,9 °C
f)	Initial boiling point and boiling range	> 100 °C
g)	Flash point	275 °C at ca.1.013 hPa - Pensky-Martens closed cup - DIN 51758
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	No data available

k)	Vapor pressure	< 1,4 hPa at 20 °C
l)	Vapor density	No data available
m)	Density	1,1 g/cm3 at 25 °C
	Relative density	No data available
n)	Water solubility	0,0002 g/l at 20 °C - OECD Test Guideline 105
o)	Partition coefficient: n-octanol/water	No data available
p)	Autoignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: ca.400 mPa.s at 25 °C
s)	Explosive properties	No data available
t)	Oxidizing properties	none

9.2 Other safety information
No data available

SECTION 10: Stability and reactivity

10.1 Reactivity
Forms explosive mixtures with air on intense heating.
A range from approx. 15 Kelvin below the flash point is to be rated as critical.

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
Violent reactions possible with:
Strong oxidizing agents

10.4 Conditions to avoid
Strong heating.

10.5 Incompatible materials
No data available

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - 38.900 mg/kg
Remarks: (External MSDS)
LC50 Inhalation - Rat - male and female - 4 h - > 5,1 mg/l - dust/mist

(OECD Test Guideline 403)
Remarks: Limit Test
(highest concentration to be prepared)
Dermal: No data available

Skin corrosion/irritation
Skin - Rabbit
Result: No skin irritation - 4 h
(OECD Test Guideline 404)

Serious eye damage/eye irritation
No data available

Respiratory or skin sensitization
Maximization Test - Guinea pig
Result: Does not cause skin sensitization.
(OECD Test Guideline 406)

Germ cell mutagenicity
Test Type: Ames test
Test system: Escherichia coli/Salmonella typhimurium
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 471
Result: negative

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

Hazardous properties cannot be excluded but are unlikely when the product is handled appropriately.

Handle in accordance with good industrial hygiene and safety practice.

SECTION 12: Ecological information

12.1 Toxicity

Toxicity to fish	static test LL50 - Danio rerio (zebra fish) - > 100 mg/l - 96 h (OECD Test Guideline 203)
Toxicity to daphnia	EC50 - Daphnia - > 10 mg/l - 48 h

and other aquatic invertebrates	Remarks: (above the solubility limit in the test medium) (Lit.)
Toxicity to bacteria	microtox test EC50 - Bacteria - 146 - 774 mg/l - 5 min Remarks: (Lit.)

12.2 Persistence and degradability

Biodegradability: aerobic - Exposure time 28 d
Result: > 60 % - Readily biodegradable.
(OECD Test Guideline 301F)

12.3 Bioaccumulative potential

No data available

12.4 Mobility in soil

No data available

12.5 Results of PBT and vPvB assessment

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Endocrine disrupting properties

No data available

12.7 Other adverse effects

Discharge into the environment must be avoided.

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product

See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number

ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name

ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)

ADR/RID: - IMDG: - IATA: -

14.4 Packaging group

ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards

ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

Further information
Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

15.2 Chemical Safety Assessment

For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Further information
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

The branding on the header and/or footer of this document may temporarily not visually match the product purchased as we transition our branding. However, all of the information in the document regarding the product remains unchanged and matches the product ordered. For further information please contact mlsbranding@sial.com.

Poloxamer 188

SAFC®

www.sigmaaldrich.com

SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 8.2
Revision Date 20.01.2021
Print Date 05.05.2022
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : Poloxamer 188 EMPROVE® EXPERT (stabilized with 70ppm BHT) Ph Eur,NF

Product Number : 1.37112
Catalogue No. : 137112
Brand : Millipore
REACH No. : A registration number is not available for this substance as the substance or its uses are exempted from registration, the annual tonnage does not require a registration or the registration is envisaged for a later registration deadline.
CAS-No. : 9003-11-6

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Pharmaceutical production

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich Chemie GmbH
Eschenstrasse 5
D-82024 TAUFKIRCHEN

Telephone : +49 (0)89 6513-1130
Fax : +49 (0)89 6513-1161
E-mail address : technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone # : 0800 181 7059 (CHEMTREC Deutschland)
+49 (0)696 43508409 (CHEMTREC weltweit)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

Formula	:	(C3H6O.C2H4O)x
CAS-No.	:	9003-11-6
EC-No.	:	618-355-0

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first-aid measures

If inhaled
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Water Foam Carbon dioxide (CO2) Dry powder

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Nature of decomposition products not known.
Combustible.
Development of hazardous combustion gases or vapours possible in the event of fire.

5.3 Advice for firefighters
In the event of fire, wear self-contained breathing apparatus.

5.4 Further information
Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Do not breathe vapors, aerosols. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up with liquid-absorbent material (e.g. Chemizorb®). Dispose of properly. Clean up affected area.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed.

Store at +2°C to +25°C.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Full contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min

Material tested:KCL 741 Dermatril® L

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Respiratory protection
Not required; except in case of aerosol formation.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: solid Color: white
b)	Odor	No data available
c)	Odor Threshold	No data available
d)	pH	6,0 - 7
e)	Melting point/freezing point	Melting point: 56 °C
f)	Initial boiling point and boiling range	> 149 °C
g)	Flash point	Not applicable
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	No data available
k)	Vapor pressure	< 0,1 hPa at 25 °C
l)	Vapor density	No data available
m)	Relative density	1,06 g/cm³ at 25 °C
n)	Water solubility	No data available
o)	Partition coefficient: n-octanol/water	No data available
p)	Autoignition temperature	No data available
q)	Decomposition	No data available

temperature

r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information

Bulk density	1.050 kg/m³

SECTION 10: Stability and reactivity

10.1 Reactivity
No data available

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .
Contains the following stabilizer(s):
butyl hydroxytoluene (BHT) (<=0,01250,0124 %)

10.3 Possibility of hazardous reactions
Violent reactions possible with:
Strong oxidizing agents

10.4 Conditions to avoid
no information available

10.5 Incompatible materials
No data available

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - 5.700 mg/kg
Remarks:
(RTECS)

Skin corrosion/irritation
No data available

Serious eye damage/eye irritation
Eyes - Rabbit
Result: No eye irritation
(OECD Test Guideline 405)

Respiratory or skin sensitization
- Rabbit
Result: Did not cause sensitization on laboratory animals.

Germ cell mutagenicity
Tests on bacterial or mammalian cell cultures did not show mutagenic effects.

Carcinogenicity

IARC: No ingredient of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information
Not available

Effects due to ingestion may include:, Diarrhea, Weakness
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

SECTION 12: Ecological information

12.1 Toxicity
No data available

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Other adverse effects
No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number

ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name

ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)

ADR/RID: - IMDG: - IATA: -

14.4 Packaging group

ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards

ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

Further information

Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

National legislation

Seveso III: Directive 2012/18/EU of the European Parliament and of the Council on the control of major-accident hazards involving dangerous substances.

Not applicable

15.2 Chemical Safety Assessment

For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

L-Arginine HCl

SAFC®

www.sigmaaldrich.com

SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 8.2
Revision Date 21.03.2021
Print Date 05.05.2022
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : L-Arginine monohydrochloride EMPROVE® EXPERT Ph Eur,BP,ChP,JP,USP

Product Number : 1.01544
Catalogue No. : 101544
Brand : Millipore
REACH No. : 01-2119961765-25-XXXX
CAS-No. : 1119-34-2

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Pharmaceutical production

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich Chemie GmbH
Eschenstrasse 5
D-82024 TAUFKIRCHEN

Telephone : +49 (0)89 6513-1130
Fax : +49 (0)89 6513-1161
E-mail address : technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone # : 0800 181 7059 (CHEMTREC Deutschland)
+49 (0)696 43508409 (CHEMTREC weltweit)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

Formula	:	C6H14N4O2 · HCl
Molecular weight	:	210,67 g/mol
CAS-No.	:	1119-34-2
EC-No.	:	214-275-1

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first-aid measures

If inhaled
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Water Foam Carbon dioxide (CO2) Dry powder

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Carbon oxides
Nitrogen oxides (NOx)
Hydrogen chloride gas
Combustible.
Fire may cause evolution of:
Hydrogen chloride gas, nitrous gases, nitrogen oxides
Development of hazardous combustion gases or vapours possible in the event of fire.

5.3 Advice for firefighters
In the event of fire, wear self-contained breathing apparatus.

5.4 Further information
Suppress (knock down) gases/vapors/mists with a water spray jet. Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Avoid inhalation of dusts. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up dry. Dispose of properly. Clean up affected area. Avoid generation of dusts.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed. Dry.

Recommended storage temperature see product label.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Respiratory protection
required when dusts are generated.
Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.
Recommended Filter type: Filter type P1

The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: solid Color: white
b)	Odor	odorless
c)	Odor Threshold	Not applicable
d)	pH	5,5 - 7 at 211 g/l at 25 °C
e)	Melting point/freezing point	Melting point: > 235 °C at ca.1.013 hPa - Decomposes before melting.
f)	Initial boiling point and boiling range	ca.235 °C at ca.1.013 hPa - Decomposes on heating.
g)	Flash point	No data available
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	The product is not flammable. - Flammability (solids)
j)	Upper/lower flammability or	No data available

	explosive limits	
k)	Vapor pressure	< 0,0 hPa at 20 °C - OECD Test Guideline 104
l)	Vapor density	No data available
m)	Relative density	No data available
n)	Water solubility	ca.730 g/l at 20 °C - completely soluble
o)	Partition coefficient: n-octanol/water	log Pow: -3,24 at 25 °C - (calculated) - Bioaccumulation is not expected.
p)	Autoignition temperature	does not ignite
q)	Decomposition temperature	No data available
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information

Bulk density	ca.1.250 kg/m3
Particle size	126,3 µm - OECD Test Guideline 110 - Mean particle size

SECTION 10: Stability and reactivity

10.1 Reactivity
The following applies in general to flammable organic substances and mixtures: in correspondingly fine distribution, when whirled up a dust explosion potential may generally be assumed.

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
Violent reactions possible with:
Strong oxidizing agents

10.4 Conditions to avoid
no information available

10.5 Incompatible materials
No data available

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - male and female - 12.400 mg/kg
Remarks: (ECHA)

Skin corrosion/irritation
Skin - reconstructed human epidermis (RhE)
Result: No skin irritation
(OECD Test Guideline 439)

Serious eye damage/eye irritation
Eyes - Rabbit
Result: No eye irritation - 1 h
(OECD Test Guideline 405)

Respiratory or skin sensitization
No data available

Germ cell mutagenicity

Test Type: Mutagenicity (mammal cell test): chromosome aberration.
Test system: Human lymphocytes
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 473
Result: negative
Remarks: (in analogy to similar products)
The value is given in analogy to the following substances: L-Arginine
Test Type: Ames test
Test system: Escherichia coli/Salmonella typhimurium
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 471
Result: negative
Remarks: (in analogy to similar products)
The value is given in analogy to the following substances: L-Arginine

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

Repeated dose toxicity - Rat - male - Oral - 13 Weeks - NOAEL (No observed adverse effect level) - 3.130,9 mg/kgRemarks:
(ECHA)

Repeated dose toxicity - Rat - female - Oral - 13 Weeks - NOAEL (No observed adverse effect level) - 3.565,1 mg/kgRemarks:

(ECHA)

Not available

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

SECTION 12: Ecological information

12.1 Toxicity

Toxicity to fish	semi-static test LC50 - Danio rerio (zebra fish) - 2.800 mg/l - 96 h (OECD Test Guideline 203) Remarks: (in analogy to similar products) The value is given in analogy to the following substances: L-Arginine
Toxicity to bacteria	Remarks: (in analogy to similar products) The value is given in analogy to the following substances: L-Arginine (L-arginine monohydrochloride)

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Other adverse effects
No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number
ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name
ADR/RID: Not dangerous goods
IMDG: Not dangerous goods

IATA: Not dangerous goods

14.3 Transport hazard class(es)
ADR/RID: - IMDG: - IATA: -

14.4 Packaging group
ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards
ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

Further information
Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture
This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

National legislation
Seveso III: Directive 2012/18/EU of the European Parliament and of the Council on the control of major-accident hazards involving dangerous substances. : Not applicable

15.2 Chemical Safety Assessment
For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Further information
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

The branding on the header and/or footer of this document may temporarily not visually match the product purchased as we transition our branding. However, all of the information in the document regarding the product remains unchanged and matches the product ordered. For further information please contact mlsbranding@sial.com.

Sucrose

Sigma-Aldrich.

www.sigmaaldrich.com

SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 6.5
Revision Date 17.04.2021
Print Date 05.05.2022
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name	:	Sucrose
Product Number	:	84097
Brand	:	Sigma
REACH No.	:	A registration number is not available for this substance as the substance or its uses are exempted from registration, the annual tonnage does not require a registration or the registration is envisaged for a later registration deadline.
CAS-No.	:	57-50-1

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses	:	Laboratory chemicals, Manufacture of substances

1.3 Details of the supplier of the safety data sheet

Company	:	Sigma-Aldrich Chemie GmbH Eschenstrasse 5 D-82024 TAUFKIRCHEN
Telephone	:	+49 (0)89 6513-1130
Fax	:	+49 (0)89 6513-1161
E-mail address	:	technischerservice@merckgroup.com

1.4 Emergency telephone

Emergency Phone #	:	0800 181 7059 (CHEMTREC Deutschland) +49 (0)696 43508409 (CHEMTREC weltweit)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No 1272/2008.

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

May form explosible dust-air mixture if dispersed.

SECTION 3: Composition/information on ingredients

3.1 Substances

Synonyms	:	α-D-Glucopyranosyl β-D-fructofuranoside
Formula	:	$C_{12}H_{22}O_{11}$
Molecular weight	:	342,30 g/mol
CAS-No.	:	57-50-1
EC-No.	:	200-334-9

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first-aid measures

If inhaled
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Water Foam Carbon dioxide (CO2) Dry powder

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Carbon oxides
Combustible.
Development of hazardous combustion gases or vapours possible in the event of fire.

5.3 Advice for firefighters
In the event of fire, wear self-contained breathing apparatus.

5.4 Further information
Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Avoid inhalation of dusts. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up dry. Dispose of properly. Clean up affected area. Avoid generation of dusts.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed. Dry.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Full contact

Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:KCL 741 Dermatril® L

Respiratory protection
required when dusts are generated.
Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.
Recommended Filter type: Filter type P1

The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: crystalline Color: white
b)	Odor	No data available
c)	Odor Threshold	No data available
d)	pH	5,5 - 7,5 at 342 g/l at 25 °C
e)	Melting point/freezing point	Melting point/range: 185 - 187 °C
f)	Initial boiling point and boiling range	697,11 °C at 1.013,3 hPa
g)	Flash point	Not applicable
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	May form combustible dust concentrations in air.
j)	Upper/lower flammability or explosive limits	No data available

k)	Vapor pressure	No data available
l)	Vapor density	No data available
m)	Relative density	No data available
n)	Water solubility	342 g/l at 20 °C - completely soluble
o)	Partition coefficient: n-octanol/water	log Pow: -3,277
p)	Autoignition temperature	No data available
q)	Decomposition temperature	160 - 165 °C -
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information
No data available

SECTION 10: Stability and reactivity

10.1 Reactivity
The following applies in general to flammable organic substances and mixtures: in correspondingly fine distribution, when whirled up a dust explosion potential may generally be assumed.

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
Violent reactions possible with:
Strong oxidizing agents

10.4 Conditions to avoid
no information available

10.5 Incompatible materials
No data available

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - 29.700 mg/kg
Remarks: Behavioral:Somnolence (general depressed activity).CyanosisDiarrhea

Skin corrosion/irritation
No data available

Serious eye damage/eye irritation
No data available

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Test Type: Mutagenicity (mammal cell test):
Result: negative
Remarks: (National Toxicology Program)

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information
RTECS: WN6500000

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

Substances which occur in nature

Hazardous properties cannot be excluded but are unlikely when the product is handled appropriately.

Handle in accordance with good industrial hygiene and safety practice.

SECTION 12: Ecological information

12.1 Toxicity
No data available

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Other adverse effects
No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions.

SECTION 14: Transport information

14.1 UN number
ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name
ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)
ADR/RID: - IMDG: - IATA: -

14.4 Packaging group
ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards
ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

Further information
Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture
This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

National legislation
Seveso III: Directive 2012/18/EU of the European Parliament and of the Council on the : Not applicable

control of major-accident hazards involving dangerous substances.

: Not applicable

15.2 Chemical Safety Assessment
For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Further information
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

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