UiT
THE ARCTIC UNIVERSITY OF NORWAY

Faculty of Health Sciences
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Stability of analgesic admixtures

Degradation and compatibility of common compounds in singular and binary admixtures in use for palliative treatment

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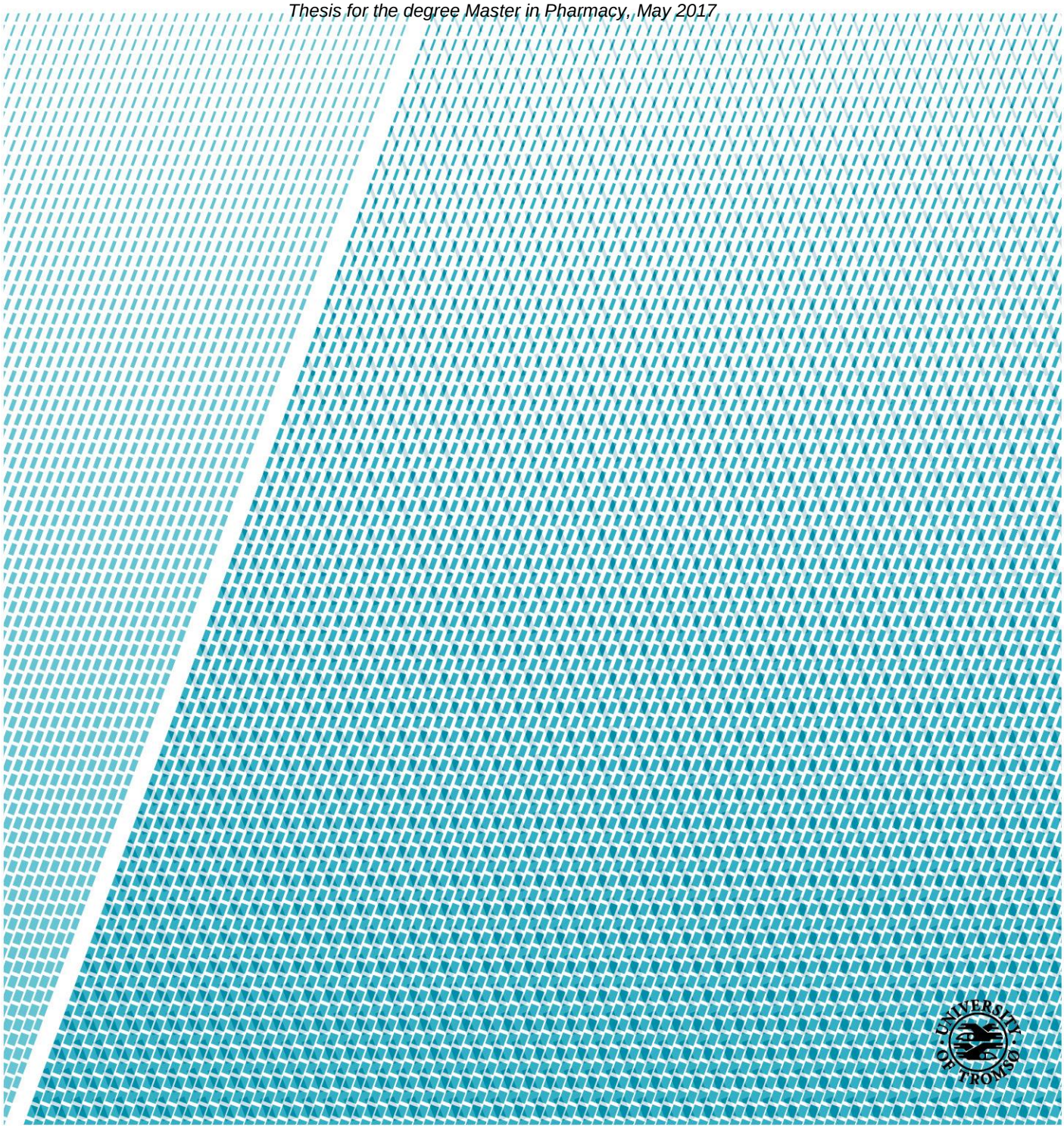

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List of Abbreviations

Abbreviation	English
ACN	Acetonitrile
I.S.	Internal standard
IFA	Department of Pharmacy
PCAD	Patient-controlled analgesia device
SPC	Summary of Product Characteristics
TFA	Trifluoroacetic acid

Acknowledgements

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- Anne Christine Koveland

Abstract

AIM: The aim of this study was to investigate whether common compounds used in analgesic admixtures will remain physically and chemically stable after 3 weeks (22 days) under different storage conditions.

METHODS: 23 admixtures in total were prepared aseptically at the hospital pharmacy in Tromsø. The following compounds used were diluted in 0.9 % NaCl: morphine hydrochloride (1 and 35 mg/mL), oxycodone hydrochloride (0.5 and 8 mg/mL), hydromorphone hydrochloride (1 and 40 mg/mL), haloperidol lactate (0.01 and 1 mg/mL) and midazolam hydrochloride (0.01 and 1 mg/mL) for injection. Singular and binary admixtures of the compounds in low and high concentrations were stored in glass vials or PVC cassettes in different locations with different temperatures: At 4 °C protected from light, in room temperature protected from light, room temperature with presence of fluorescent light and at 37 °C protected from light to simulate an accelerated stability study. The admixtures were analyzed by high performance liquid chromatography with UV-detection (HPLC-UV) on day of production (day 0) and day 8, 15 and 22 after production.

RESULTS: Almost all the admixtures did not show any sign of precipitation or color change after 22 days, but there were a few exceptions: Admixtures with high concentrations of morphine, hydromorphone and oxycodone tended to get some yellowing when stored at 37 °C, while precipitation occurred in haloperidol 1 mg/mL after 15 days when stored at 4 °C. No relevant additional peaks to the compounds tested were detected on the chromatograms. The singular and binary admixtures had to a greater or lesser extent of fluctuating degradation profiles almost all over the test period.

CONCLUSION: This study demonstrates the compatibility of morphine, oxycodone and hydromorphone in low and high concentrations, in combination with haloperidol with low and high concentrations, or midazolam with low concentration diluted in 0.9 % NaCl. Admixtures produced for palliative use should be stored in room temperature protected from light to avoid precipitation. The chemical stability of the admixtures was challenging to conclude, due to technical issues. At times, there were large deviations in the results, making the degradation profiles of the admixtures uncertain. The results should therefore not be used to set a longer expiry date on the produced admixtures. It is highly recommended to redo the experiments with another operator, laboratory and instrumentation to confirm or enlighten the results in this study.

KEYWORDS: Stability, compatibility, morphine hydrochloride, oxycodone hydrochloride, hydromorphone hydrochloride, midazolam hydrochloride, haloperidol lactate, glass vials, CADD-cassettes, HPLC-UV

1 Introduction

1.1 Background

Analgesic admixtures are often given to cancer patients with severe pain, to patients with post-operative pain, or in situations where oral administration is not possible or difficult. Many patients suffer from several symptoms, like pain, nausea and anxiety simultaneously. The admixtures may therefore consist of several compounds like analgesics, antiemetics, anticholinergics or sedatives where the composition and dose are individualized to each patient.

There are very strict requirements for production and to quality for any drug product which is to be injected. To ensure the quality, the admixtures are prepared aseptically. With this technique, the tentative expiry date can therefore, compared to admixtures prepared by non-aseptically technique, be prolonged. One usually assumes that the microbial aspect is safe due to the aseptic production methods and the quality of the preparations used in the production.

There are in general few previous studies on stability-testing of admixtures with more than one drug, especially over long-term periods like several weeks. Due to a wide range of possible combinations and concentrations of the compounds, data on stability for any admixture are desired, but especially long-term stability data may come in handy. It is therefore in great interest to investigate the compatibility and stability for admixtures in all concentrations. New documentation may contribute to better patient safety in the future.

This is the first stability project on analgesic admixtures done at the hospital pharmacy in Tromsø and will be considered as an introductory study. Hopefully, this project may create a foundation for further stability studies on this highly clinical relevant field.

1.1.1 Patient-controlled analgesia devices

The admixtures are prepared in a patient-controlled analgesia device (PCAD) and allows the patient to self-administer injectable drugs, even at their home, when oral administration is not an alternative or difficult to achieve. The drugs are administered subcutaneously. A PCAD consists of a reservoir and a pump. The reservoir is made of plastic and usually contains 50, 100 or 250 mL fluid. The PCAD was introduced in 1970 (1, 2), and is generally considered safe and effective in use for cancer pain and post-operative pain(3, 4). The drugs are diluted in a suitable solvent, e.g. 0.9 % sodium chloride or 5 % glucose and prepared in cassettes made for the PCAD. The physician in charge sets the speed of the infusion in maximum amount per hour (e.g. mg/h), and is sometimes allowing some loading doses in addition depending on the patient's amount of breakthrough pain.

The PCAD allows the palliative patients to be treated at home, and may for some be the preferred way to spend their last time. The subcutaneous administration of opioid admixtures quickly relieves pain compared to oral administration, and the rate of effectiveness is high (5).

1.1.2 The economical and logistical aspect

The distances from hospital to where people live on the countryside are often quite far in Norway, especially in Northern Norway. Patients who live far away and get the PCAD treatment at their home, need to get the PCAD transported or sent by mail service, which may take several days. These days are in addition to the already short known shelf life, depending on the admixture.

The new Coordination Reform for health services in Norway encourages treatment in the local community if possible to avoid long hospital stays, to free resources and shorten hospital queues (6). The hospital pharmacy in Tromsø produces admixtures both for hospital wards and for use in home care. Fewer productions per week per patient may simplify the logistics considerably, as well as increase the capacity and free more resources. Stability studies of admixtures may be an investment for the future, if the results indicate that fewer productions are needed while the patient still gets the essential pain management.

As the life expectancy gets higher, the pressure on the hospitals and other health care institutions are expected to increase in the years to come. It is likely that the increasing number of elderly will require more productions at the hospital pharmacy than in the present. It is therefore in great interest to gather information about possible future productions as early as possible to be in advance of the need.

To maintain the patients' well-being in the best possible way is the most important task in health care. Many palliative patients want to be in their own home during the last time of their life, and spend it with their family members around them and to be in safe and familiar environments. The disease itself stresses many people out, and both short and long hospital stays may be an additional source of stress.

1.1.3 Common containers

Injections can be distributed in numerous containers depending on their administration site, physical properties and storage conditions. The fact that the material of the container does not interact with the drug is most important when choosing container.

Containers made of glass have been used for hundreds of years because of its properties. Glass is completely impermeable for vapour and is very suitable for heat sterilization,

unlike plastics. Examples of glass containers can be ampoules, vials and bottles. When adding iron oxide in the glass, amber colour occurs, which is used to prevent the drug from ultra violet light. It is four main types of glass qualities, based on their reactivity properties (7).

- Type I glass is neutral. The material is called borosilicate glass which is the least reactive of the four glass types. Vials and ampoules used for parenteral drugs are often made of type I glass.
- Type II glass are cheaper than type I glass, and not that chemical resistant relatively to type I. It is used for the most compounds except for blood products and aqueous solutions with pH = 7 or higher.
- Type III glass is suitable for non-aqueous parenterals (e.g. powder for injection) and non-parenterals. This type of glass has better hydrolytical resitance than type IV, which is how they are distinguished.
- Type IV glass have the lowest hydrolytic resitance. It is not suitable for injections, but can be used for solids (e.g. tablets) or semi-solids (e.g. ointments or creams) (7).

Containers for parenteral administration made of different plastics, for example polyethylene, polypropylene and polyvinyl chloride (PVC) are very common today (7, 8). Plasticizers, e.g. dioctylphtalate, are added to PVC to get the desired properties. The plasticizers are used to increase the plastic's flexibility, like in infusion bags and tubing. Infusion bags and syringes made of polyethylene and polypropylene are widely used for cytostatic injections given at hospitals. The reservoirs used for analgesic admixtures are often made of PVC. Concerning plastic containers, a potential problem is that they sometimes are permeable to vapour, leading to a possible more concentrated drug solution over time (7).

The containers, both glass and plastic, must be impermeable to microorganisms after closure. Different types of closures can be rubber stoppers (natural or artificial) which are well suited to form seals, or plastic closures. Each type of closure has its advantages and disadvantages. Natural rubber reseals itself even after several piercings of a needle, making it suitable for multiple-use for injectable products (e.g. when several admixtures are produced at the same time, but to different patients). The disadvantages with natural rubber is that it can become brittle over time, and they are not suited for multiple autoclaving. In addition, gas and moisture permeation may occur. Artificial rubber, on the other hand, tend to have the opposite properties; it is less permeable to gas and moisture and can undergo multiple autoclaving, but should not be exposed to more than one needle insertion due to more rigid quality. Thus, it can lead to small fragments of rubber into the drug solution, which is not desirable (7).

1.1.4 Common stability problems in aqueous solutions

During storage time, one or several stability problems may occur and affect the quality and efficacy of the pharmaceutical(s). Problems regarding stability in solutions or admixtures includes chemical and physical ones. The physical stability problems include

- Shedding of particles
- Adsorption to or absorption into container
- Extraction of materials into liquid from container
- Evaporation(7)

One of the most common phenomena is precipitation and is characterized by formation of crystals in the liquid. The crystals can consist of either the drug itself or its degradation products. Precipitation varies with variables like pH-value, temperature and concentration of the compounds and/or the excipients. The consequences are poor appearance, but most of all a serious risk of potential harm to the patient if administered. In every occasion when precipitation occurs during production or storage, the admixture will be discarded immediately in the interest of patient safety.

Drug molecules can adsorb to the walls or closures of the container, while drug molecules can be absorbed into the walls or closures. The effect on the drug product will thus be loss of drug, contributing to lack of effect when administered (7).

Some preservatives tend to adsorb to the small rubber stoppers that are used as closures on glass vials or syringes, and may occur especially when the concentration of the preservative is low (7). This does not just lead to poor appearance, but also potential reduced preservation ability.

Physical changes in solutions may be easy to spot, but chemical instability on the other hand can be problematic, since the changes in most cases not are visible to the human eye. Physical changes often indicate that chemical changes also have taken place. Chemical issues include hydrolysis, oxidation and light sensitivity. Hydrolysis is a common cause of degradation in aqueous solutions, which involves breaking bonds in chemicals using water (7). Another common degradation cause is oxidation, where free radicals reacts in presence of oxygen and often lead to several phases of the reaction (7).

Dimerization and polymerization are results of reactions between two or more of the same molecule, forming dimers (two molecules reacting) or polymers (more than two molecules reacting). These reactions may be initiated by ultraviolet light or just occur over time.

1.1.5 Stability testing of aqueous solutions

Analgesic admixtures made for use in PCAD are considered as a "new drug product", even though they are made of drug products themselves (the drugs for injection and diluents). Stability testing requirements for new drug products are based on guidelines from the International Conference on Harmonization (ICH) (9, 10).The maximum acceptable loss of drug is usually down to 90 % of its theoretical concentration (7), but it depends on the active pharmaceutical ingredient and its properties.

Stability tests are performed to estimate the shelf life for formulated pharmaceutical products. Different temperatures and storage conditions may influence the shelf life of the drug, and several tests simulating the actual storage conditions are done. The gold standard is testing in room temperature for the whole amount of time, and in the exact packaging that the drug product is going to be distributed in. Accelerated stability testing or stress testing are performed to simulate extreme conditions of e.g. heat and relative humidity, and to force the drug solution to degrade. This can be done in many ways, e.g. expose the drug solutions to temperatures of 50-60 °C or higher, doing temperature cycles or expose it to ultraviolet light (9, 11).

New drug products that are going to be marketed undergo long-term stability tests that simulate different "worst case scenarios" of climatic zones in the different parts of the world. ICH operates with 4 different climatic zones with different temperatures (21 °C – 31 °C) and percent relative humidity (60 % - 70 %). Norway has a so-called temperate climatic zone where standard room temperature is 21 °C. Normally, humidity has little influence on the stability of the drug product unless the test drug is hygroscopic or if it is in solid form, like tablets.

During stability testing, minimum 3 batches are tested to evaluate any difference between them. The individual shelf-life for each batch is calculated, and the "final" shelf-life are based on the shortest individual one.

1.1.6 The compounds in general - what is known about their stability in admixtures?

The compounds to be studied are morphine, oxycodone, hydromorphone, haloperidol and midazolam. All compounds except for haloperidol are in the hydrochloride salt form. Especially morphine and haloperidol are frequently combined drugs in palliative medicine (12).

1.1.6.1 Morphine

Morphine is an opiate derived from the opium poppy, *Papaver somniferum*. It is one of the most well-known analgesic agents today, and therefore one of the most studied compounds. The drug can be administered almost at all routes and is usually given as a sulphate or hydrochloride salt. The degradation products and the kinetics have been studied (13, 14). Morphine degrades by dimerization to mainly pseudomorphine in aqueous solutions and in presence of oxygen, but in small amounts over years when undiluted (15). A study from 1932 reported deadly outcome on rabbits and dogs where extremely high doses of pseudomorphine were injected intravenously: 25 and 60 mg/kg, respectively, but is not found to be effective nor toxic to animals when given orally or subcutaneously (16).

Admixtures with high concentrations in the range of 10 mg/mL to 30 mg/mL with 0.9 % NaCl as diluent, stored at 22°C are found to be stable for up to 3 months (17).

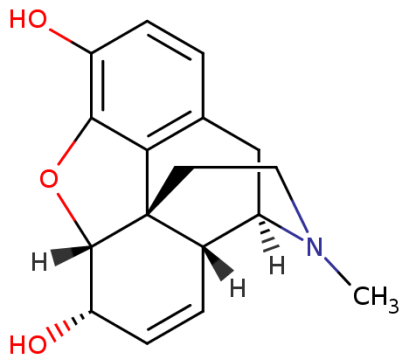

Figure 1 – Morphine(18)

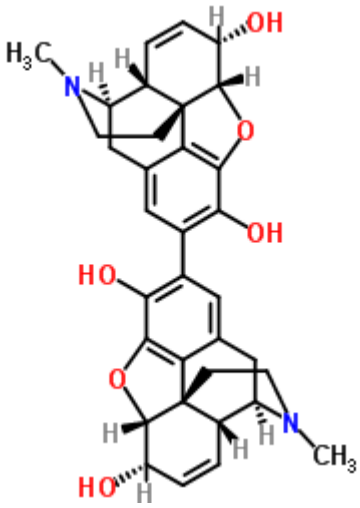

Figure 2 – Pseudomorphine (18)

1.1.6.2 Oxycodone

Oxycodone is an opioid analgesic with an effect similar to morphine, and is used for opioid sensitive pain such as cancer pain (19). Few studies on stability of oxycodone in admixtures have so far been conducted. There are found up to 9 degradation products of oxycodone in an accelerated stability test, where the pH- value was 12.8 (20), and at very high temperature at 93 °C. It is not known if any of the degradation products are toxic.

Oxycodone have been shown to be stable in 0.9 % NaCl, sterile water and 5 % glucose for up to 28 days when stored in ambient temperature (25 °C) and prepared aseptically (21). Another study shows that oxycodone hydrochloride in concentrations of 5, 50 and 100 mg/mL is stable for 35 days(20), with sterile water as diluent. Oxycodone is also visually compatible with haloperidol for at least 7 days (22), which is going to be a combination to be tested in this study.

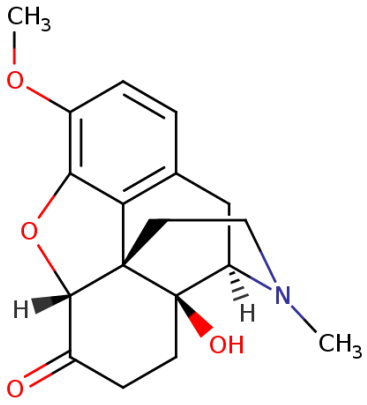

Figure 3 – Oxycodone (18)

1.1.6.3 Hydromorphone

Hydromorphone is a semi-synthetic derivative of morphine and is used for severe pain. It is about 8.5 times more potent than morphine when given intravenously, and side-effects like nausea, vomiting and sedation are less likely to occur compared to administration of morphine (23). Hydromorphone may be used as an alternative to morphine.

With 0.9 % NaCl as additive, hydromorphone HCl in concentrations of 1.5 mg/mL and 80 mg/mL in plastic syringes is found to be stable for 60 days (24). The only study found so far using a PCAD- reservoir concluded that hydromorphone in saline is chemically stable and sterile for up to 16 weeks when prepared aseptically (25).

There are few stability studies including hydromorphone with other drugs, but it is found to be stable in 0.9 % NaCl for at least 7 days in combination with ketamine in various concentrations in glass vials (26). A combination of reconstituted hydromorphone hydrochloride and haloperidol lactate in 5 % dextrose with concentrations of 0.2 mg/mL

and 0.5 mg/mL, respectively, is reported to be physically compatible for at least 48 hours at 22°C in glass vials (27). The same study reports compatibility with midazolam (0.2 mg/mL) with the conditions already mentioned. The chemical stability of hydromorphone HCl and midazolam HCl have also been studied (28), with the result of under 7 % loss of both drugs in 23 days at, and below, ambient temperature.

The Summary of Product Characteristics (SPC) for hydromorphone hydrochloride (Palladon®, Mundipharma) states that there are no physical incompatibilities in combination with both low and high concentrations of haloperidol or midazolam hydrochloride, which are used in this project, over 24 hours (29). The certain concentrations, however, are not mentioned.

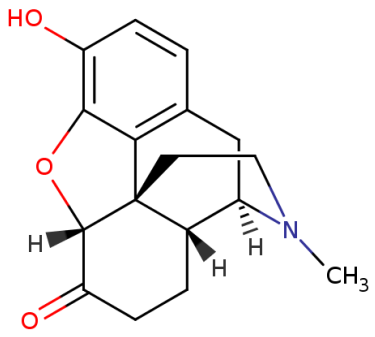

Figure 4 – Hydromorphone (18)

1.1.6.4 Midazolam

Midazolam is a sedative agent used in palliative care for anxiety and cramps. It degrades in presence of daylight, mainly to desalkylflurazepam (an active metabolite) and should therefore be stored in dark (30).

Both undiluted (5 mg/mL) and diluted midazolam (0,5 mg/mL in 0.9 % NaCl) has been found to be visually compatible and stable for 36 days at temperatures of 4, 25 and 40 °C protected from light (31). Several other studies of midazolam in various concentrations from 0,03 mg/mL to 1 mg/mL are reported to be visually compatible with NaCl (32, 33).

Midazolam "B. Braun", which is used in this project have a pH value of 2.9 – 3.7. Midazolam hydrochloride is highly water soluble at pH 4 or less, and lipid solubility increase with higher pH (34).

Binary and ternary admixtures with midazolam, regardless of concentration, produced in the hospital pharmacy in Tromsø currently have a set expiry date of 5 days after production (35).

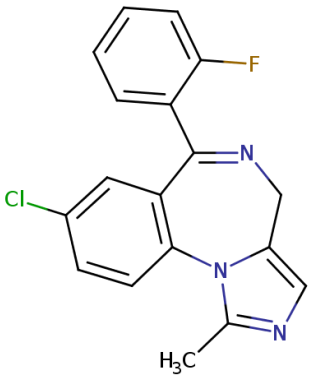

Figure 5 - Midazolam(18)

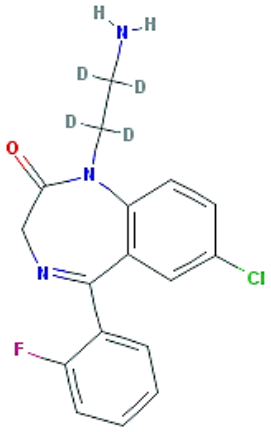

Figure 6 – Desalkylflurazepam (18)

1.1.6.5 Haloperidol

Haloperidol is a 1st generation antipsychotic with antiemetic and motility-enhancing effect which is considered useful in combination with opiates and opioids causing constipation.

Liquid for injection are stored in dark glass ampoules to protect the drug from light.

Haloperidol is found to be visually stable in 0.9 % NaCl with concentration of haloperidol up to 0.75 mg/mL for up to 7 days (36), and compatible with different morphine concentrations for 7 days (37). Concentrations of haloperidol over 1 mg/mL have shown to form precipitate in 0.9 % NaCl (38) and it has been concluded that 5 % dextrose is the preferred solvent for high concentrations of haloperidol because of its lesser risk of forming precipitation (36).

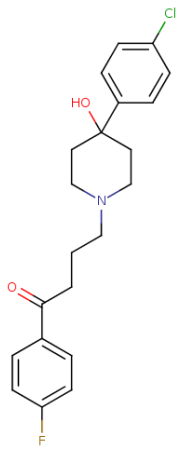

Figure 7 - Haloperidol (18)

1.1.7 High Performance Liquid Chromatography

A high performance liquid chromatograph mainly consists of a pump (solvent delivery system), an injector, a column with packing material and a detector as shown in **Figure 8**. The pump sucks the mobile phase from the reservoir and pumps it through the column with high pressure and a certain flow rate chosen by the operator. The sample solution from the vial is injected into the continuous flow. The sample then goes through the column. Depending on the properties of the packing material in the column, the mobile phase and the analyte altogether, the analyte will adsorb to the column (the stationary phase) for a while and then eluate with the mobile phase. The detector will detect at what time the analytes eluate, sending the information to the computer software which generates a chromatogram with peaks of all the detectable compounds.

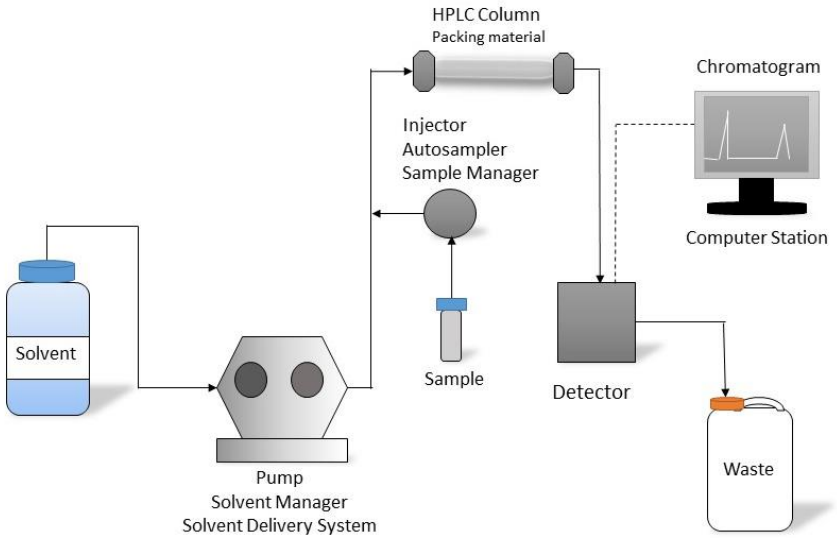

Figure 8 - Schematic view of the HPLC system. Adapted and modified from (1).

The mobile phases in HPLC have numerous compositions, but in general there are one aqueous mobile phase containing H_2O and one organic mobile phase, such as acetonitrile or methanol. The composition of the mobile phases is adapted to the analytes' properties (polarity and retention time), and the elution can be isocratic or gradient. Isocratic means that the composition of the mobile phase(s) does not change during the analytical process, and in a gradient elution the composition changes over time. A gradient is sometimes necessary when the elution lasts for too long or when certain compounds do not eluate because of their lipid solubility.

A reversed-phase column is used in this project, which has a stationary phase containing silica particles modified with long alkyl chains, normally ranging from 4 carbons (C4) to 18 carbons (C18). The stationary phase is hydrophobic, meaning that lipophilic compounds will adsorb to the column for a while, and the hydrophilic compounds will go

faster through the column. The compounds in this project are suitable for HPLC analysis because of their solubility.

A known volume of an internal standard (I.S.) is added to each sample solution to correct for sample loss which may occur in all stages of the analytical process. The ratio of peak area of the analyte and I.S. is used in the calibration process and to determine the concentration of analyte in the sample solution. The I.S. is preferred to resemble the analytes, but needs to be separated from all of them (39). The I.S. in this project is (R)-(+)-propranolol hydrochloride which is suitable because of its wide absorption range in the UV-spectrum.

1.1.8 Photo diode array versus conventional UV-detector

The detector that is used in this study is a photo diode array (PDA). The PDA can generate a spectrum through the whole wavelength range, unlike the UV-detector where the wavelength needs to be fixed in advance. With the spectrum from the PDA, it is possible to find absorption maximum for several compounds in the same test solution, and the baseline stability is better, meaning less noise in the chromatogram (39).

A lot of substances can absorb ultraviolet (UV) light in the range of 200-800 nm wavelength. To absorb UV-light, the analyte molecules need to contain at least one chromophore, which means an UV-light absorbing functional group like a double bond or triple bond (39). All the analytes in this project have at least one absorbing group, in this case several double bonds, making this type a suitable choice of detector.

1.1.9 Validation and performance characteristics

The point of validation of a method is to ensure that the results are reliable. The validation guidelines are based on documents from the International Conference on Harmonization (ICH), where methods for performance characteristics like precision, accuracy, linearity and range, and detection limit are described (40).

Specificity of the method is to ensure that the analyte is being detected, and not impurities or degradation products. If there is a lack of specificity in the method, this may be complimented with other performance characteristics.

Precision is a measure of the degree of reproducibility or repeatability of the analytical method, and can be obtained by 1) using the same sample, under same conditions and using the same instrumentation, or 2) using inter- and intraday precision.

Limit of detection and quantification is normally a crucial point in analytical methods, however in this special case, the probable lowest concentration of any of the compounds in these admixtures may be down to 25 % of target concentration. But, if any of the compounds degrade to 25 % of target concentration, they will regardless be discarded, so no lower limit is necessary yet.

Calibration curves for each compound indicating the linearity need to be made to ensure the measured concentration. The concentration of each compound can be calculated using the $y=ax + b$ formula obtained from the calibration curve. The linearity coefficient (R^2) should ideally be close to 1, but lower values can be accepted depending on the analysis (39).

1.1.10 Outliers

All data sets may contain "extreme" values, called outliers, which may affect the results drastically. Eventual outliers will be calculated with Dixon's Q-test (41):

$$Q_{calculated} = \frac{gap}{range} = \frac{|Xi - Xcritical|}{|X1 - Xcritical|}$$

Where X_i is the value closest to $X_{critical,}$ which is the value desired to be discarded. X_1 is the highest or lowest value in the analytical series, depending on which value X_i is. X_1 is the value farthest from $X_{critical}$. $X_{critical}$ will be discarded if the Q-value is high enough according to the Q-test table (41), indicating that $X_{critical}$ is an outlier. The more available parallels, the lower is the limit values.

2 Research aim

The aim of this study is to investigate the long-term stability of different analgesic and/or sedative compounds used in PCAD, and then create degradation profiles for the compounds. Singular and binary admixtures with low and high concentrations are to be stored in glass vials and/or CADD cassettes before being analysed by HPLC. Hopefully, the results obtained from this preliminary study will indicate if continuous studies are necessary, or eventually, indicate which admixture combinations that should be studied further or not.

When a suitable method is established, the hospital pharmacy may have an opportunity to go through with smaller stability studies on certain admixtures when needed.

3 Hypothesis

The admixtures will perform differently upon storage depending on the different concentrations and different drugs in the mixture.

Due to light sensitivity of haloperidol, it is conceivable that the admixtures containing haloperidol will degrade increasingly in presence of light compared to those protected from light.

High concentrations of haloperidol (1 mg/mL and higher) in 0.9 % NaCl may form precipitate, based on former stability studies (36, 38, 42). The preferred solvent for haloperidol is 5 % dextrose (36), but the solvent in this project will be 0.9 % NaCl and may in combination with other drugs like morphine, oxycodone and haloperidol not form precipitate.

Admixtures stored in refrigerator may form precipitate more often compared to those stored in room- or high temperature.

4 Materials and Methods

4.1 HPLC

The instrumentation used was Alliance 2695 separations module (Waters) controlled by Empower Pro. The column was a reverse-phase SunFire C-18 3,5 µm, 3,0 x 50 mm (Part no. 188002542, Serial no. 0107735188128 02). The temperature in the column oven was always 35°C, and the temperature in the sample chamber was 5°C.

In general, 2 different gradients were used in this project depending on whether the admixture to be analysed contained midazolam or not. **Table 1** shows the initial gradient that were used in a short period, but it was later altered to save some time, as shown in **Table 2.**

10 µL of sample was injected into the HPLC for every analysis, and there were 2 injections for each parallel.

Table 1 - Initial gradient used for admixtures without midazolam

Time (min)	Flow (mL/min)	% A	% C
Initial	1.75	98	2
0.10	1.75	98	2
6.90	1.75	40	60
7.00	1.75	10	90
8.30	1.75	10	90
8.50	1.75	98	2

Table 2 - Final gradient used for admixtures without midazolam

Time (min)	Flow (mL/min)	% A	% C
Initial	1.75	98	2
0.10	1.75	98	2
4.50	1.75	65	35
4.60	1.75	10	90
5.80	1.75	10	90
6.00	1.75	98	2

Table 3 - Gradient used for admixtures with midazolam

Time (min)	Flow (mL/min)	% A	% C
Initial	1.75	98	2
0.10	1.75	98	2
3.00	1.75	70	30
4.00	1.75	30	70
4.20	1.75	10	90
5.90	1.75	10	90
6.00	1.75	98	2

4.2 Chemicals

The only water used in this project was Milli-Q water. Wherever it says "H_2O" refers to Milli-Q water. The mobile phases were always prepared in 1000 mL borosilicate bottles. TFA is added to prevent "tailing" on the peaks in the chromatogram.

The following mobile phases were used for singular and binary admixtures without midazolam:

- Mobile phase A – 100 % H_2O + 0.1 % TFA (1 mL TFA in 1000 mL H_2O).
- Mobile phase C – 100 % ACN (CAS: 75-05-8) + 0.1 % TFA (1 mL TFA in 1000 mL ACN).
- Mobile phase D – 30 % H2O + 70 % MeOH (Sigma-Aldrich) for purging of injector after sample set run.

For admixtures containing midazolam, the following mobile phases were used:

- Mobile phase A – 20 mM ammonium acetate (CH_3COONH_4)- buffer:
  1.54 g of 98 % ammonium acetate (Merck) were dissolved in 100% H_2O in a 1000 mL volumetric flask and pH-adjusted to 7.4 (±0.03) with 25% ammonia solution (VWR) and/or 100 % acetic acid (Sigma-Aldrich).
- Mobile phase C – 100 % ACN
- Mobile phase D – 30 % H_2O + 70 % MeOH for purging of injector.

30 % H_2O + 70 % MeOH were used for needle wash after every injection.

4.2.1 Internal standard

For admixtures without midazolam, (R)-(+)-propranolol hydrochloride (Sigma-Aldrich) dissolved in mobile phase A (100 % H_2O + 0.1 % TFA) was used. The concentration was 0.250 mg/mL. For admixtures with midazolam, the I.S. was (R)-(+)-propranolol hydrochloride dissolved in 100 % H_2O with the concentration of 0.250 mg/mL.

4.2.2 Standard solutions

Table 4 - Materials used in the making of standard solutions

Material	Supplier	Lot	Expiry date	CAS-number
Morphine, 1 mg/mL in methanol	Sigma-Aldrich	FE08141515	11/20	57-27-2
Oxycodone, 1 mg/mL in methanol	Sigma-Aldrich	FE01081501	02/20	76-42-6
Hydromorphone, 1 mg/mL in methanol	Sigma-Aldrich	FE04101502	06/20	466-99-9
Haloperidol, 1 mg/mL in methanol	Sigma-Aldrich	FN02241502	03/20	52-86-8
Midazolam, 1 mg/mL in methanol	Sigma-Aldrich	FE11111402	03/20	59467-70-8
100 % H_2O + 0.1 % TFA	Produced at IFA	-	-	-
20 mM CH_3COONH_4 - buffer	Produced at IFA	-	-	-

The compounds in the standard solutions had two different target concentrations. Morphine, oxycodone and hydromorphone had a target concentration of 50 µg/mL. The target concentration for haloperidol and midazolam was 10 µg/mL. A triplicate with dilutions of 200 %, 150 %, 100 %, 75 %, 50 % and 25 % of target concentrations (see **Table 5**) were made by adding the standard solutions to 0,5 mL safe lock tubes. 340 µL of H_2O + TFA were added to a safe lock tube, and then the drug solutions (10 µL of haloperidol + 50 µL of hydromorphone + 50 µL of oxycodone + 50 µL of morphine).

Table 5 - Concentrations of the standard solutions

% of target concentration	Concentration for morphine, hydromorphone and oxycodone (µg/mL)	Concentration for haloperidol and midazolam (µg/mL)
25 %	12,5	2,5
50 %	25	5
75 %	37,5	7,5
100 %	50	10
150 %	75	15
200 %	100	20

4.3 Making of admixtures in isolator

All the admixtures were prepared aseptically in the "Isolator 2" located in the cytostatic laboratory at the hospital pharmacy in Tromsø. All the batch numbers of the produced admixtures were written in a production journal located at the hospital pharmacy.

Before every production, the isolator was cleaned with 70 % ethanol to prevent contamination not only from bacteria, but also from eventual cytostatics in case the isolator had been used to prepare this earlier the same day.

All equipment (outer packaging for sterile gloves, cloths etc.), drug vials or ampoules were sprayed with 70 % ethanol before insertion to the isolator. The admixtures were thereafter made according to the pharmacy's working sheets (see **Appendix III**

4.3.1 Drugs and equipment

Table 6 - Pharmaceuticals used for production of the admixtures.

Drug/solvent	Cons.	Trade name	Manufacturer
Morphine hydrochloride	40 mg/mL	Morfin NAF u/konserveringsmiddel inj. (without preservatives)	Serviceproduksjon
Oxycodone hydrochloride	10 mg/mL	OxyNorm® inj.	Mundipharma
Haloperidol lactate	5 mg/mL	Haldol® inj.	Janssen-Cilag
Hydromorphone hydrochloride	50 mg/mL	Palladon® inj.	Mundipharma
Sodium chloride, isotonic, pH = 5	9 mg/mL (0.9 %)	Natriumklorid inj.	Fresenius Kabi

Table 7 - Other equipment used for production of the admixtures.

Other equipment	Manufacturer	Comments
Syringes	Terumo	Sizes used: 1, 3, 5, 10, 20 and 50 mL
Needles	BD	Various sizes used
Filter needles	BD	-
Sterile filters	BD	-
Sterile vials, glass, 10 ml	Apodan	-
Sterile vials, glass, 20 ml and 100 ml	-	Sterilized by the hospital pharmacy in Tromsø
CADD®- cassettes, 50 ml		-
Rubber stoppers		Sterilized by the hospital pharmacy in Tromsø
Injection hoods, not peelable	Den Norske Eterfabrikk	-
Shackles for light protection	-	-

4.4 Storage conditions

After production of the admixtures, the glass vials (12 in total) were marked with date of analysis, that were on day 8, 15 and 22 from the date of production. Then they were placed in 3 different locations with different temperatures. 3 vials were placed in a refrigerator at 4°C. 6 vials (3 without light protection and 3 with light protection) were placed in the laminar flow hood in the analytical laboratory at IFA at 21-22 °C and the fluorescent light were turned on during the whole storage time. 3 vials were placed in a heating cabinet at 37°C without presence of light.

The admixture to be analysed at date of production (day 0) were kept protected from light after production and prepared for HPLC within 1-2 hours.

Initially attempts were made to leave the light turned on in the refrigerator and in the heating cabinet as well, also with 3 vials on each. The tiny lamp in the refrigerator lighted very slightly, unlike in the heating cabinet where a regular office lamp (18 W and 50 Hz) was placed. The attempt with light in the fridge was ended eventually because of time issues in addition to presumed less clinical relevance.

4.5 Sample preparation

Table 8 - Equipment and chemicals used for sample preparation

Equipment or chemical	Size or range	Manufacturer	Lot no.
Micropipettes	0.5 – 10 µL	Eppendorf	-
	10 – 100 µL		
	100 – 1000 µL		
Safe lock tubes	0.5 mL	Eppendorf	-
	1,5 mL		
Tips for micropipettes	0,1 – 10 µL	VWR	-
	10 – 100 µL	VWR	
	100 – 1000 µL	Finntip	
Borosilicate bottles	1000 mL	VWR	-
Vortex, model V1	-	IKA	-
Trifluoro acetic acid (TFA)	25 mL	Sigma-Aldrich	STBG1988V
98 % CH_3COONH_4	1 kg	Merck	616CC500816
Milli-Q water	-	Millipore	-

On the day of analysis (day 8, 15 or 22), all the vials were evaluated visually for colour change and precipitation. Then they were allowed to reach ambient temperature. The different admixtures were diluted in triplicates for each storage condition to their target concentration in 0.5 or 1.5 mL safe lock tubes (**Figure 9**). **Table 9** shows how the different admixtures were diluted to reach their target concentrations. The admixtures that contained 2 compounds had to be diluted in two rounds, meaning that the procedure in **Figure 9** was repeated for the actual admixture.

80 µL of the dilutions were thereafter transferred to the HPLC- vials, and 10 µL of I.S. was added to each vial. The vials were labelled with day of analysis, storage condition, compound(s) they contained and if it was low or high concentration from the original glass vial.

Table 9 - Dilution of the admixtures

Target concentration (µg/mL): 50

* Altered concentration of morphine hcl in one admixture

Compound (X)	Salt factor	Concentration of (X) hydrochloride in admixture		Concentration of compound in admixture		Need of more than 1 dilution?	"Middle" dilution Concentration (µg/mL): 1000 µL of admixture	µL of mobile phase A	Dilution µL of admixture/ "middle" dilution	µL of mobile phase A
		mg/mL	µg/mL	mg/mL	µg/mL					
Morphine L	0.887	1	1000	0.89	887	No			28.2	471.8
Morphine H	0.887	35	35000	31.05	31045	Yes	16.1	483.9	25	475
Morphine H*	0.887	32	32000	28.38	28384	Yes	17.6	482.4	25	475
Hydromorphone L	0.887	1	1000	0.89	887	No			28.2	471.8
Hydromorphone H	0.887	40	40000	35.48	35480	Yes	14.1	485.9	25	475
Oxycodone L	0.9	0.5	500	0.45	450	No			55.6	444.4
Oxycodone H	0.9	8	8000	7.2	7200	No			3.5	496.5

Target concentration (µg/mL): 10

Compound (X)	Salt factor	Concentration of (X) hydrochloride in admixture		Concentration of compound in admixture		Need of more than 1 dilution?*	*Concentration after "middle dilution" (µg/mL)	"Middle dilution" µL of admixture	µL of mobile phase A	µL of admixture/ "middle" dilution	µL of mobile phase A
		mg/mL	µg/mL	mg/mL	µg/mL						
Midazolam L	0.9	0.01	11.11	0.01	10	No				500	0.0
Midazolam H	0.9	4.44	4444.44	4	4000	Yes	200	25.0	475.0	25	475.0
Haloperidol L	1	0.01	10.00	0.01	10	No				500	0.0
Haloperidol H	1	1.00	1000.00	1	1000	No				5	495.0

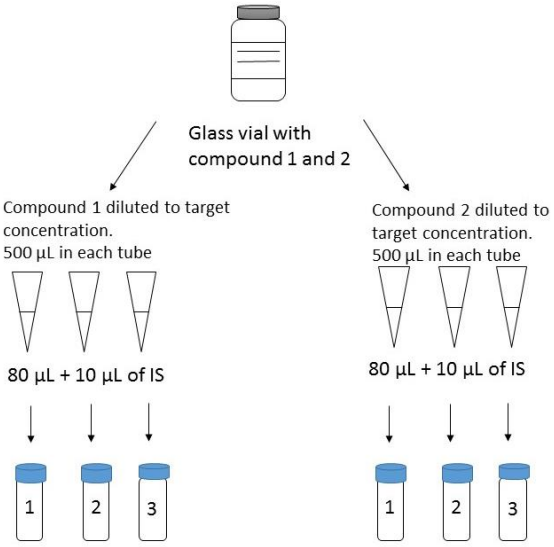

Figure 9 – How each admixture which different storage conditions was diluted

5 Results and Discussion

A total of 23 admixtures have been tested in this project period. Regarding the stability of all the admixtures in the different storage conditions, it is a great amount of information which have been obtained. Among all this information, it may most likely be reasonable to focus on the admixtures stored in room temperature and protected from light, since these storage conditions are the most common for the analgesic admixtures produced in the hospital pharmacy today. The CADD- cassettes in which the admixtures are prepared in, are made of dark PVC and have a light-protecting function.
No peaks from potential degradation products were detected in the chromatograms, at least not when the admixtures were diluted to their target concentrations.

Some of the admixtures have a higher initial concentration than 100 %, which is the theoretical and ideal concentration. However, variations always occur and almost no values will be exactly 100 %. All the admixtures were produced without a pharmacist to inspect whether exact amount of drug or diluent were pulled out correctly, which would not have taken place if the admixtures were prepared to patients. The HPLC analysis have been the "inspector" in this case.

5.1 Validation of HPLC method

5.1.1 Standard curves

There were made 3 different standard curves for the 3 gradients used in this project. Initially an attempt was made to combine all the compounds (morphine, oxycodone, hydromorphone, haloperidol, midazolam and I.S.) in one standard solution with 100 % H_2O + 0.1 % TFA as diluent. All the compounds seemed to be acceptably separated, but the area of the peak on the I.S. increased with the concentration of the standard solution. The area of the I.S. should be similar in each injection. When all the compounds were tested separately (without adding I.S.), midazolam showed two peaks. Midazolam was removed from the standard solution, and standard curves for the other compounds were made.

The values for the standard curves in **Figure 10** were extracted at 246.3 nm, because of the clearest signal of haloperidol as well as the rest of the compounds' signals were also acceptable. For **Figure 11**, the values were extracted at 230 nm.

The standard solutions were run on day 2 and 3 as well to see if there were any change in the charts. **Figure 10** shows all the injections over the 3 days combined. Separate standard curves for all the compounds on day 1, 2 and 3 were also made for comparison, and did not change significantly.

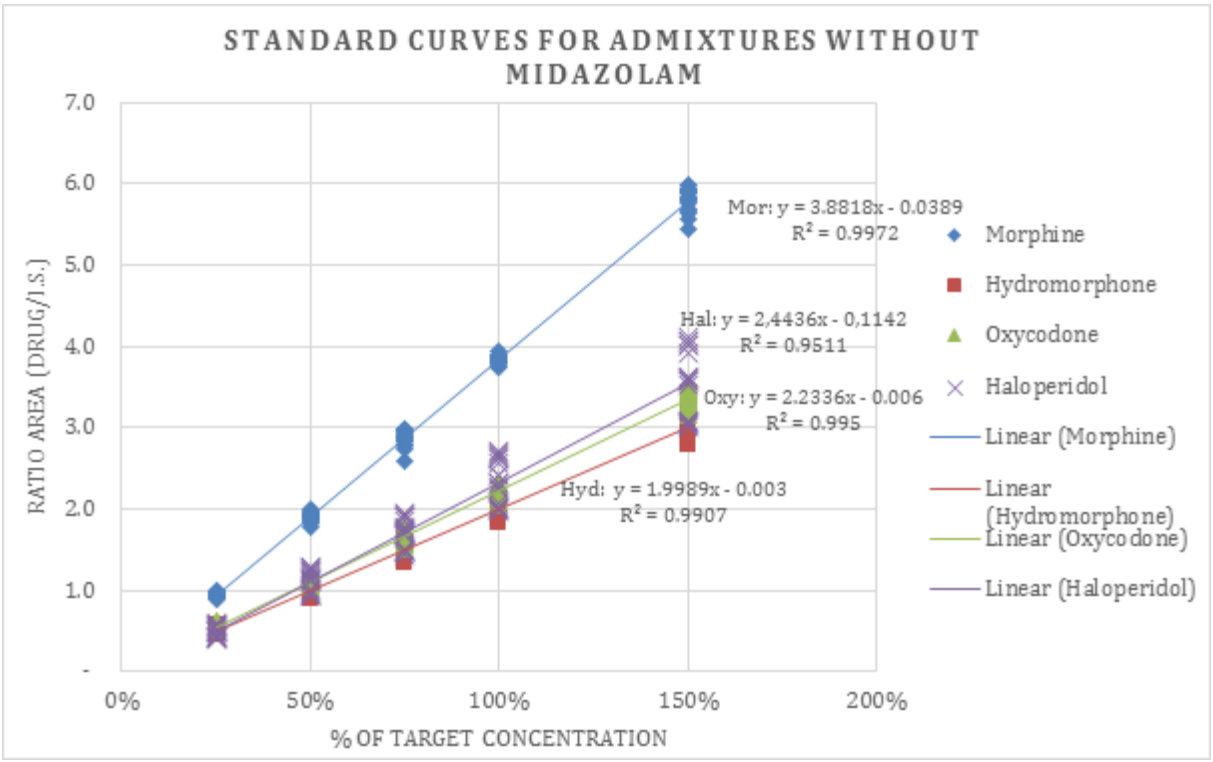

Figure 10 – Standard curves for morphine, oxycodone, hydromorphone and haloperidol

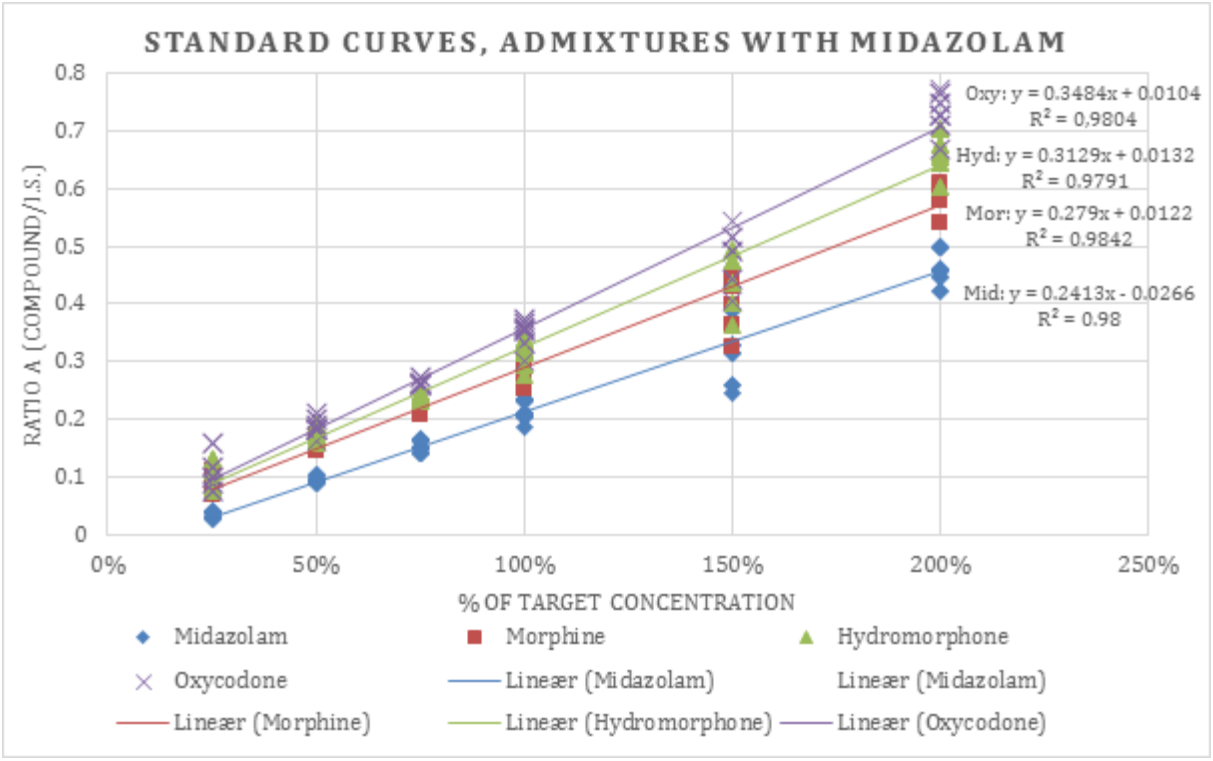

Figure 11 - Standard curves for midazolam, morphine, hydromorphone and oxycodone

5.1.2 Linearity and range

The linearity coefficient (R^2) for morphine, hydromorphone and oxycodone was relatively close to 1, while the value for haloperidol was slightly lower (see **Figure 10**). Due to this, the uncertainty of obtained haloperidol values is slightly lower than for the other compounds. Linearity have been shown for the compounds in the range of 25 % - 150 % of target concentration (12.5 – 75 µg/mL) for morphine, oxycodone and hydromorphone. For haloperidol and midazolam, the linearity is in the range of 25 – 150 % and 25 – 200 % of target concentration, respectively.

5.1.3 Precision

The repeatability of 6 determinations of a 100 %- solution gave a RSD of <5 % for the ratio of the peak area of the compounds divided with the peak area of I.S.

5.1.4 Detection limit

The lowest limit of detection for morphine, oxycodone and hydromorphone was 7.5 µg/mL, while it was 2.5 µg/mL for haloperidol and midazolam. This was done by visual evaluation of the chromatogram. Limit of detection and quantification is normally a crucial point in analytical methods, however in this special case, the probable lowest concentration of any of the compounds in these admixtures may be down to 25 % of target concentration. But, if any of the compounds degrade to 25 % of target concentration, they will regardless be discarded, so no lower limit is necessary yet.

5.1.5 Discussion of HPLC method

When the standard curves for morphine, oxycodone, hydromorphone and haloperidol were made, the standard solutions of methanol were used. Due to very little viscosity of the methanol, some difficulties with pipetting of the solutions occurred. A very small volume (only 10 µL) of haloperidol was pipetted, and the methanol tended to "adsorb" to the pipette tip when the plunger was pushed. This obviously led to differences in concentrations between the dilution series. For the other compounds, a bigger amount was pipetted. The variations between the dilution series were smaller for these compounds, but still detectable in the chart (**Figure 10**).

Acceptable and clear peaks appeared for all the standard solutions, and they were well separated. Blank samples with mobile phase A were also injected after the highest concentration of the standard solutions, and there was no sign of carry-over.

The standard curves could also have been made by adding all the standard solutions in methanol to one vial, and alter the injection volume at the HPLC to increase after 2 or 3 injections. The advantage with this method is that the results gives a good indication of the precision of the instrument. However, the drawback is that eventual errors in pipetting not will be caught up, like in the current method.

5.2 Singular admixtures in glass vials

All the results from the charts are based on average values obtained from the HPLC assay. When some of the results are described in detail, it will sometimes be used abbreviations for the storage conditions as shown in **Table 10**. The day of analysis (0, 8, 15 or 22) will be put before the eventual letter abbreviation.

Table 10 - Abbreviations used in discussion

Abbreviations	
L	Low concentration
H	High concentration
C	Stored in cold temperature (4°C) without presence of light
CL	Stored in cold temperature (4°C) and in presence of light
LR	Stored in room temperature exposed to light
DR	Stored in room temperature protected from light
W	Stored in warm temperature (37°C) without presence of light
Mor	Morphine
Oxy	Oxycodone
Hyd	Hydromorphone
Hal	Haloperidol
Mid	Midazolam

5.2.1 Morphine HCl

See **Appendix I page A and B** for all average values.

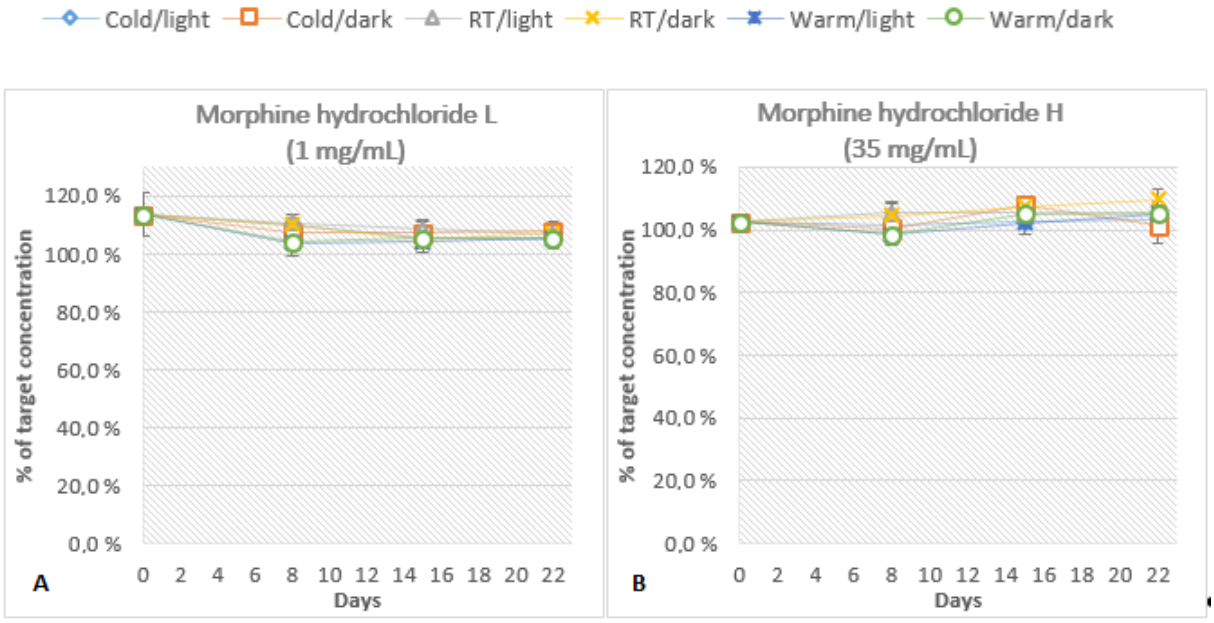

Figure 12 - Morphine HCl. A) low and B) high concentration.

No colouring or precipitation occurred after 22 days for Mor L. The initial concentration of Mor L (1 mg/mL) was in average 113.6 % (see **Figure 12A**), and the standard deviation was a bit high – 7.7 %. This was the first admixture prepared. It was only made 1 dilution (1 parallel) from the original glass vial by mistake and then transferred to 3 HPLC- vials. The less parallels, the higher the uncertainty is. Former stability studies of morphine in 0.9 % NaCl have shown that the change in morphine concentration is very little even after several months (15, 43), so it is conceivable that the measured result on day 0 was a result of the lack of parallels.

Morphine HCl H (35 mg/mL) shows, in general, no great drug loss over 22 days, which is consistent with previous finds as showed in section **1.1.6.1**. Some yellow colouring occurred after 22 days, mainly in the vials stored in presence of light regardless of temperature. The vial stored at 37°C had the greatest change in colour since the production day. The yellow colour in morphine solutions has been identified as pseudomorphine (15) and is not found to cause any severe reactions when administered subcutaneously.

Vermeire and Remon (15) reviewed that neither type of diluent, salt form, temperature, presence of light and type of container have any significant influence on morphine's long-term stability, which also seem to be the case here. There is no indication that there is a difference between stability in room temperature and light/dark for both concentrations of morphine HCl.

5.2.2 Oxycodone HCl

See **Appendix I page C and D** for all average values.

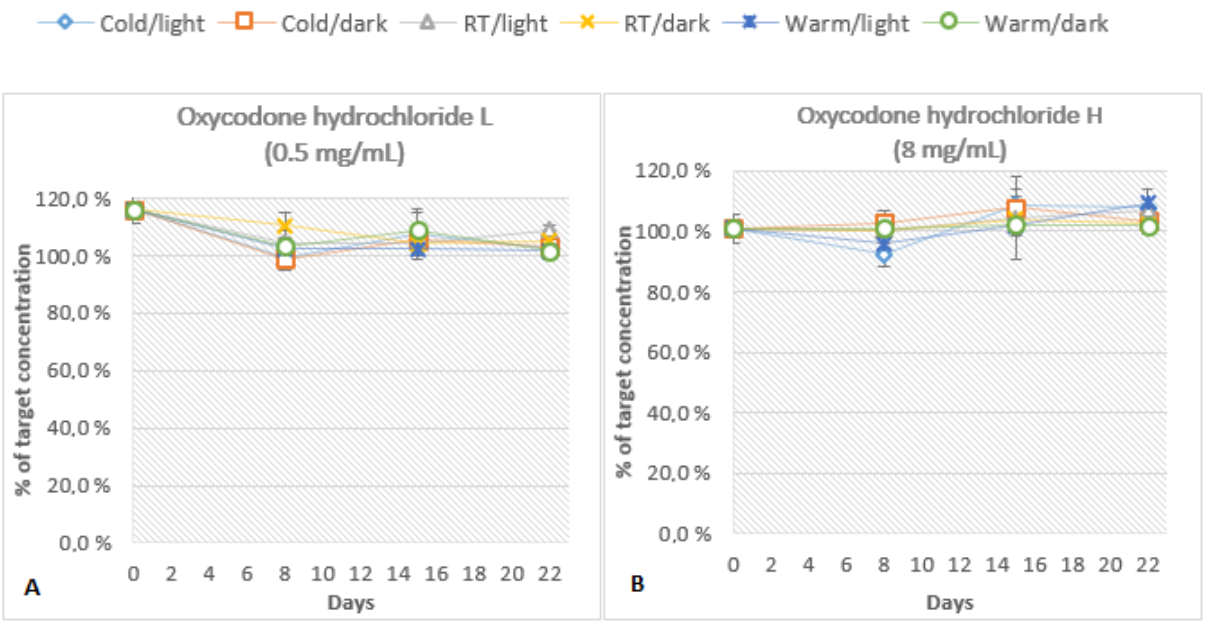

Figure 13 – Oxycodone HCl. A) low and B) high concentration.

No precipitation was observed after 22 days for all the admixtures with low and high concentration. Only Oxy L + H stored at 37 °C in light had a hint of yellow colour after day 15 and 22. All the other admixtures had no colour change after 22 days. The initial concentration of Oxy L (**Figure 13 A**) is significantly higher than the following days, where the values remained at approximately 100 % of target concentration and a few percent over.

None of the admixtures with low and high concentration reached 90 % of target concentration after 22 days, but fluctuations in concentration occurred during the storage period and the standard deviations are high, probably due to fluctuating pressure in the instrumentation or pipetting error.

If the assumption above is correct and oxycodone L is stable over 22 days, it supports a previous study from 2010 where CADD- cassettes with undiluted and diluted oxycodone were stored for 28 days, and there was no significant drug loss (21). Due to the variations in the charts, the admixtures should be retested.

5.2.3 Hydromorphone HCl

See **Appendix I page E and F** for all average values.

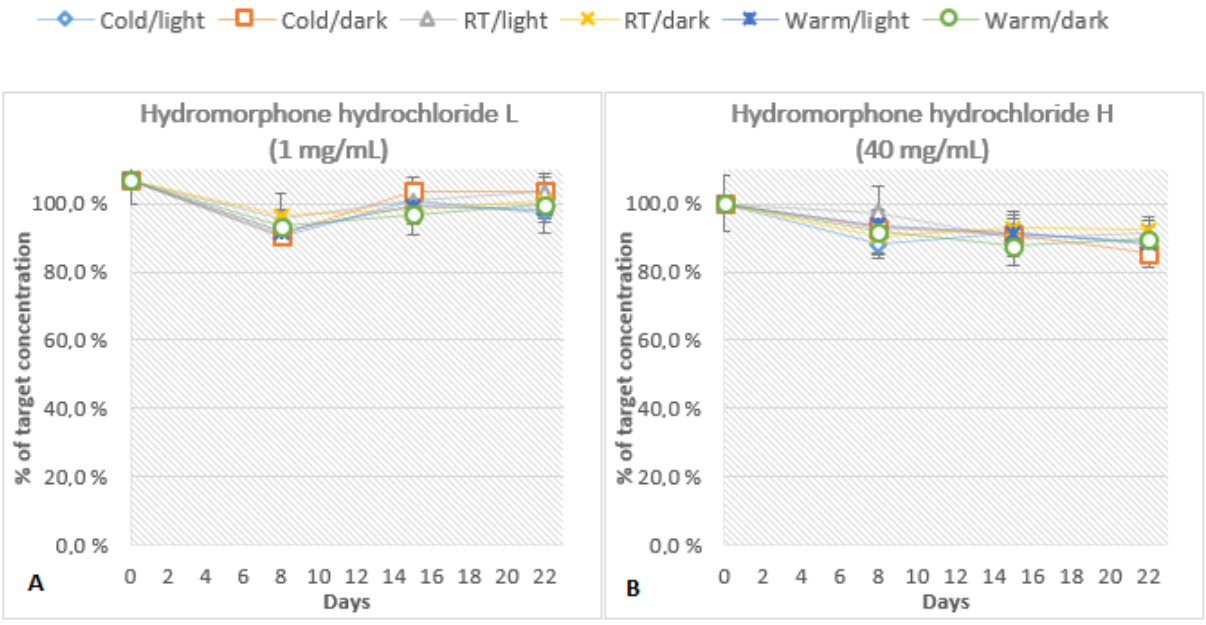

Figure 14 – Hydromorphone HCl. A) low and B) high concentration.

No precipitation or colour change was observed over 22 days for both concentrations, except from 22LW-Hyd H.

There was little loss after 22 days in general for Hyd L (**Figure 14 A**) in all storage conditions. There was a conspicuous drop in concentration after 8 days for all storage conditions, but among them, DR and LR showed least decrease.

The apparent drug loss of Hyd H (**Figure 14 B**) is slightly higher than Hyd L over time, but the standard deviations are also high for many of the values. Therefore, the results may be uncertain.

Regarding the drop in concentration on Hyd L after 8 days, it is conceivable that there were issues with either the samples or the instrument, as most of the results are not consistent with the rest. If it were the samples, it did most likely occur during the sample preparation (pipetting). Khondar et al (25) showed that hydromorphone HCl in 0.9 % NaCl was stable for 8 weeks in PVC cassettes, with 95 % of the original concentration remaining in all the samples. Because of the uncertain results, the experiments should be redone to ensure the data.

5.2.4 Haloperidol

See **Appendix I page G** for all average values.

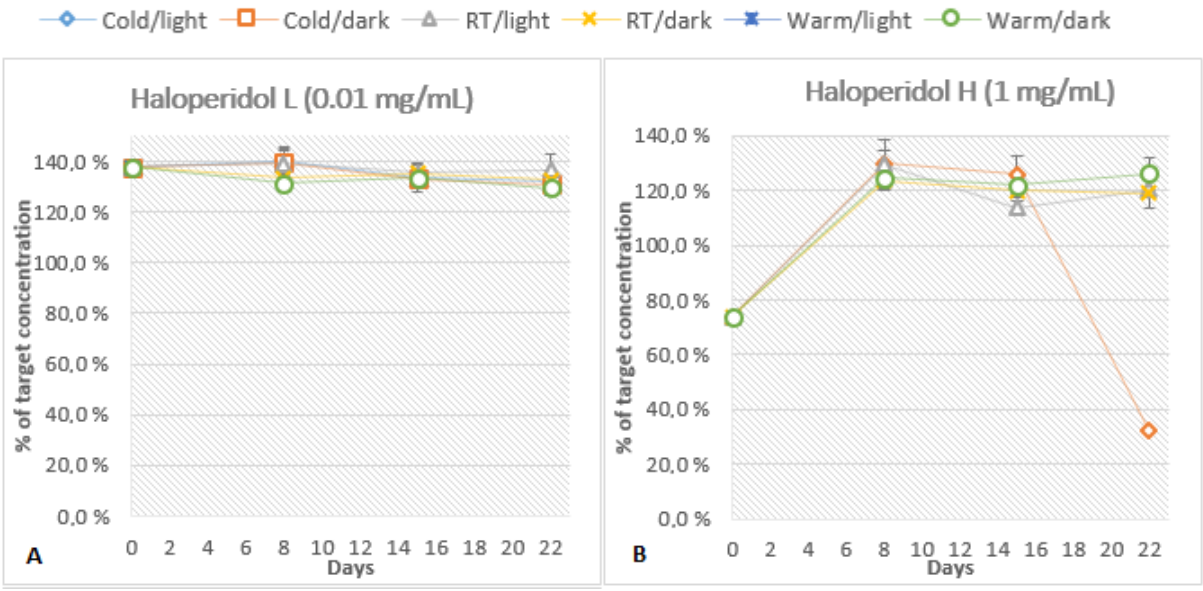

Figure 15 – Haloperidol. A) low and B) high concentration.

A slight decrease in concentration occurred in haloperidol L (**Figure 15 A**) for all storage conditions after 22 days. For the vials stored in room temperature, presence of light did not seem to have any major influence on the change in concentration. In fact, the concentration is a little bit higher in the vials stored in light than those stored in dark.

The initial concentration of haloperidol L is remarkably high – almost 140 %. This admixture was injected undiluted into the HPLC because the concentration already was at the target concentration. The explanation of the high concentration may originate from the production of the admixture, and most likely from the syringe draw technique. 0.01 mg/mL is a very low concentration, and when the admixture of haloperidol L were made, the smallest syringe (1 mL) were used for extraction of the Haldol® 5 mg/mL for injection. The syringe is graded every 0,01 mL. The amount of Haldol® to be pulled up the syringe was 0.2 mL for 100 mL of admixture in total. Operating with such low volumes can be challenging, If the plunger line is exactly at the syringe line of 0.2 mL before withdrawal, only a small mistake in the technique (e.g. an unfortunate jolt against the plunger rod) may affect the amount of volume significantly. The needle attached to the syringe will always contain a little fluid after emptying the syringe, but if there is only a little extra amount of liquid in the syringe, this may result in one extra drop from the

needle. One drop can be quite an excessive amount if the volume is already small, like in this case.

Tiny bubbles of air appear in all sizes of syringes, but they are especially challenging to get rid of in the smallest syringes. This may also affect the concentration of admixtures, especially if the concentration is very low.

At some point between day 15 and 22, precipitation occurred in haloperidol H (**Figure 15 B**) stored at 4 °C.

Haloperidol H shows quite an increase in concentration from day 0 to day 8, from 73.8 % to the range of 122.0 - 129.9 %, respectively. There was formation of precipitation in the 100- mL vial on day 0 approximately 1-2 hours after production, which may explain the apparent low initial concentration. There was nevertheless no precipitate in the other twelve 20 ml-vials. When the haloperidol admixture was prepared in the isolator, the usual procedure was followed by mixing the haloperidol injection with the 0.9 % NaCl solution in the 100 ml-vial and then disperse 5 ml of the admixture to the other 20 mL glass vials. A previous stability study where the concentration of haloperidol was 1 mg/mL in 0.9 % NaCl have shown an immediate formation of precipitate (28), but so far no records have been found that may indicate that haloperidol should react with excess air. If the glass quality of the 100- mL vial and the 20- mL vials are different, this may be a reason.

5.2.5 Midazolam HCl

See **Appendix I page H** for all average values.

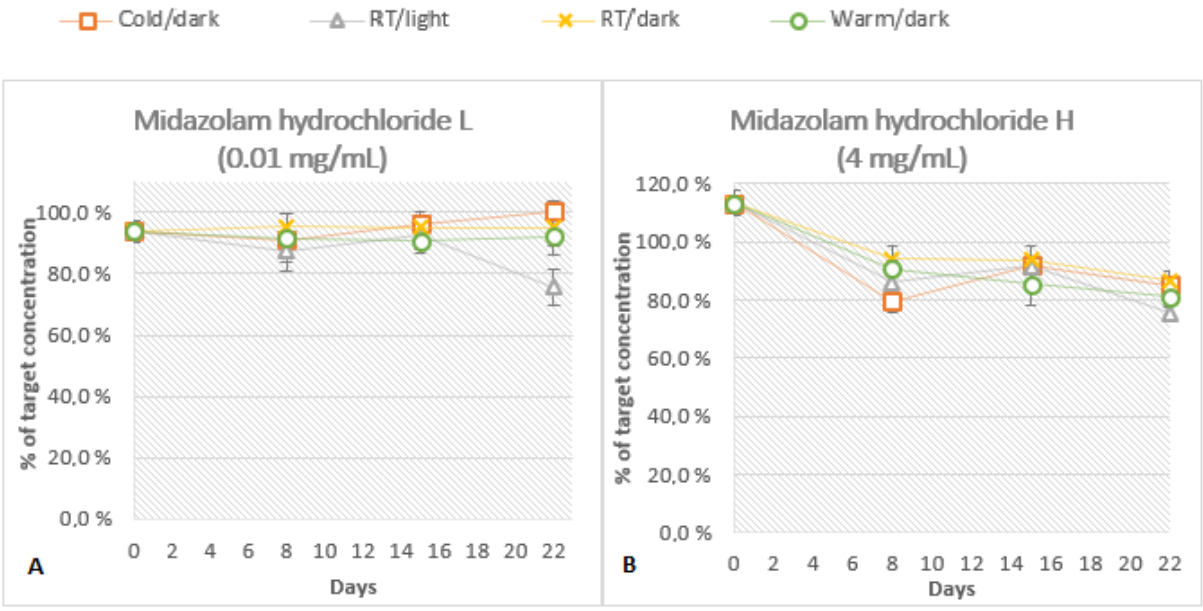

Figure 16 – Midazolam hydrochloride A) low concentration and B) high concentration.

Midazolam L (**Figure 16 A**) stored in dark at room temperature showed no drug loss in 22 days, but there was a massive drop for room temperature/light down to 75.6 %.

The initial concentration of midazolam H (**Figure 16 B**) was quite high (113.4 % in average), and there are massive drops in concentration for all storage conditions after 8 days, but the least for room temperature/light.

Midazolam has ahead of this project been considered as the most "unstable" compound of the tested ones so far. Every admixture containing midazolam has the expiry date set for 5 days (27), and more documentation regarding its stability is needed. It is probable that the method used for midazolam in this study is not optimal. Stability of midazolam have been shown in several studies in the concentration range of 0.5 mg/mL to 1 mg/mL (31, 32, 44, 45). There were little or no loss (<6 %) over stated time of 36, 49, 30 and 10 days, respectively. The midazolam admixtures, like the others above, should also be retested to confirm results due to a lot of uncertainty.

The pH in mobile phase buffer should possibly have been adjusted to 3.5, as the previous studies have been operating with this. If so, one need to assure the other components (morphine, oxycodone, hydromorphone and possibly haloperidol) also go along with the altered pH.

5.2.6 Summary of the singular admixtures

Overall, no other peaks than the compounds tested were detected.

For the admixtures stored at 37°C and in presence of light, some yellow colour occurred in almost all of them. The most noticeable cases were the ones with high concentration. Some white coating/crystals could be observed on the rubber stoppers for 15LC Mor H and 15DC Mor H, and to the greatest extent for CL.

There was no precipitation observed in the singular admixtures, except from Hal H on day 0 and day 22 at 4°C.

Mor L and H (**Figure 12**) showed little loss (about 6-7 %) of drug after 22 days regardless of storage condition, but some fluctuations did occur.

Both Oxy L + H and Hyd L + H had some fluctuations throughout the whole storage time in all storage conditions. Even though the admixtures did not seem to have a great drug loss over 22 days in total (except from Hyd H), it cannot be concluded whether the singular admixtures tolerate long-term storage when the results are so uncertain.

Midazolam in low and high concentration seemed the most unstable of the singular admixtures tested.

Based on all the values obtained, there are overall no clear trends in behaviour of the admixtures and decrease in concentration based on the different storage conditions as suggested in the hypothesis.

5.3 Singular admixtures in CADD®- cassettes

Initially, 0.9 % NaCl was filled in one 50 mL CADD® reservoir and stored over 3 weeks, and tested at day 8, 15 and 22 with the same gradient as the glass vials to see of any peaks on the chromatogram occurred. No peaks at any wavelength were identified, meaning that no apparent plasticizers from the inner reservoir leached to the solution. It is known that the plasticizer DEHP may leach from the PVC material into solutions especially in presence of certain drugs (46), but no studies indicating that any of the compounds in this project applies to this have so far been conducted.

A drawback with the dark PVC cassettes is the difficulty with observation of eventual colour changes and partly precipitation over time. The inner bag in the cassette has a pebbled appearance, and may make it challenging to spot precipitation if there only are a few particles, unlike in the glass vials. The admixtures in the cassettes had the same concentrations as those in the glass vials. It was therefore not expected any significant differences in the appearance of the admixtures between type of containers.

There was formation of tiny air bubbles to varying degrees in all the cassettes already after 8 days. The amount of bubbles was more pronounced in the admixtures with high concentrations. It is very important to get rid of all bubbles in the production of the admixtures for the safety of the patient. In the end of the production, the cassette need to be thumped against a hard surface to loosen the bubbles from the corners and the folds in the inner plastic bag. The air is then withdrawn with a syringe. Even though it looked like all bubbles were gone, the procedure may not have been thoroughly done by the operator in these cases. When several beats against the cassettes were made, more bubbles seemed to appear, so is very possible.

The possibility of evaporation is also present, but it is not known if this is a contributing factor. Bubbles did also appear in the hose, which easily could be removed by letting some of the admixture drip into a waste container.

The graphs of the admixtures in PVC cassettes can be seen in context with the admixture in glass vials, but they are not directly comparable because of the difference in container. Further tests need to be done.

5.3.1 Morphine HCl in PVC cassette

See **Appendix I page A and B** for all average values.

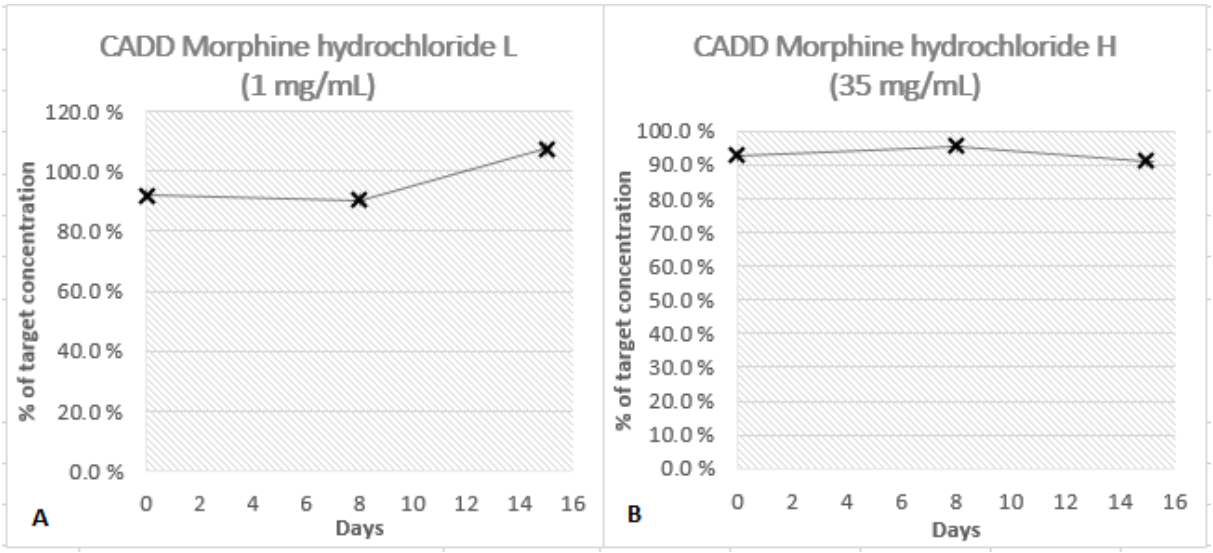

Figure 17 - Morphine hydrochloride in cassette. A) low concentration, and B) high concentration

No apparent precipitation did occur in any of the concentrations, nor any colour changes as far it was possible to spot. As discussed in 5.3, bubbles appeared in the cassette. On test day 15, only 1 value from Mor L (**Figure 17 A**) was obtained due to technical issues, making the graph deceptively increasing. Mor H (**Figure 17 B**) looks more stable over time, but a slight increase in concentration of a few percent appeared on day 8. The graphs of morphine in cassettes can be seen in context with morphine in glass vials (**Figure 12**).

5.3.2 Oxycodone HCl in PVC cassette

See Appendix I page C and D for all average values.

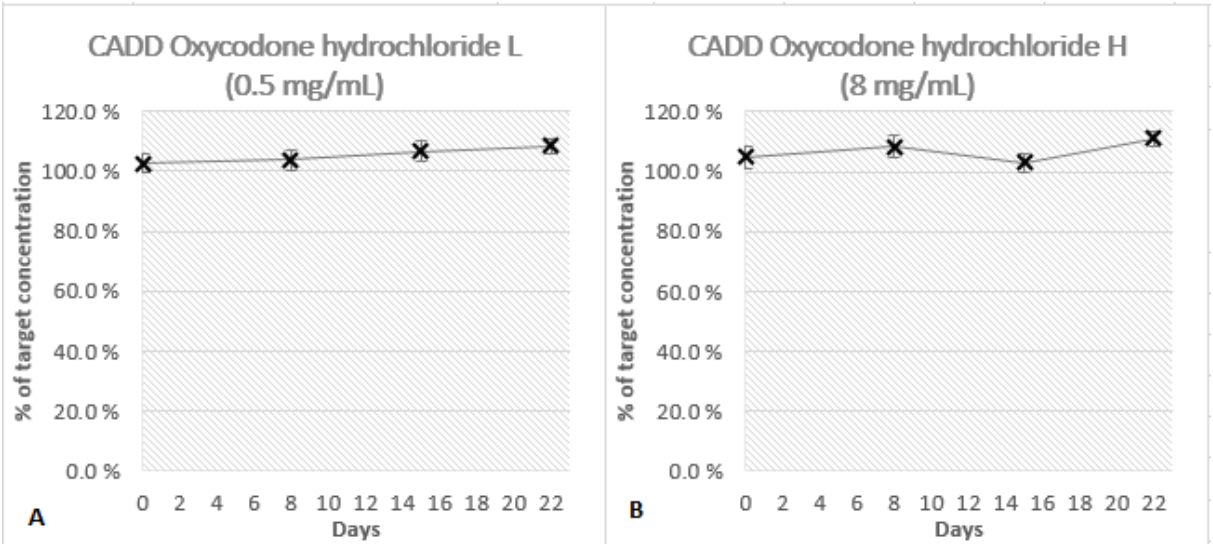

Figure 18 - Oxycodone hydrochloride in cassette A) low concentration, and B) high concentration

Oxy L and H did not have any precipitation or colour change over time, but small bubbles appeared after day 8 as already discussed. Oxy L always have a measured concentration over 100 %, but there are some fluctuations also here, especially on Oxy H. There graphs may be seen in context with **Figure 13**, but there are no clear trends in concentration change.

5.3.3 Hydromorphone HCl in PVC cassette

See Appendix I page E for all average values.

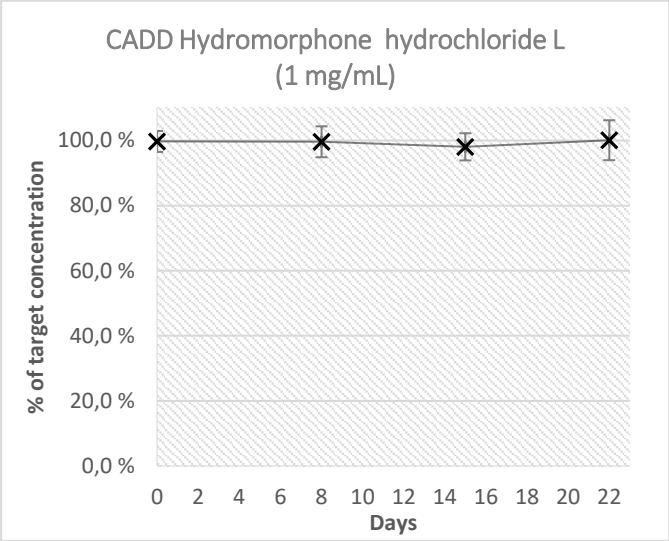

Figure 19 - Hydromorphone hydrochloride low concentration in cassette

Only one admixture with hydromorphone in PVC cassette was made. No precipitation or colour change was observed, which also was expected. There was apparently no drug loss of hydromorphone HCl after 22 days, and may indicate that hydromorphone 1 mg/mL is stable in PVC cassettes over this period. This result can be seen in the context of the previous result in glass vials (**Figure 14 A**), but even though this admixture seems stable, further tests should be done before making any conclusions.

5.4 Binary admixtures in glass vials

Abbreviations	
L	Low concentration
H	High concentration
C	Stored in cold temperature (4°C) without presence of light
CL	Stored in cold temperature (4°C) and in presence of light
LR	Stored in room temperature exposed to light
DR	Stored in room temperature protected from light
W	Stored in warm temperature (37°C) without presence of light
Mor	Morphine
Oxy	Oxycodone
Hyd	Hydromorphone
Hal	Haloperidol
Mid	Midazolam

5.4.1 Morphine HCl + haloperidol

See **Appendix II page I and J** for all average values.

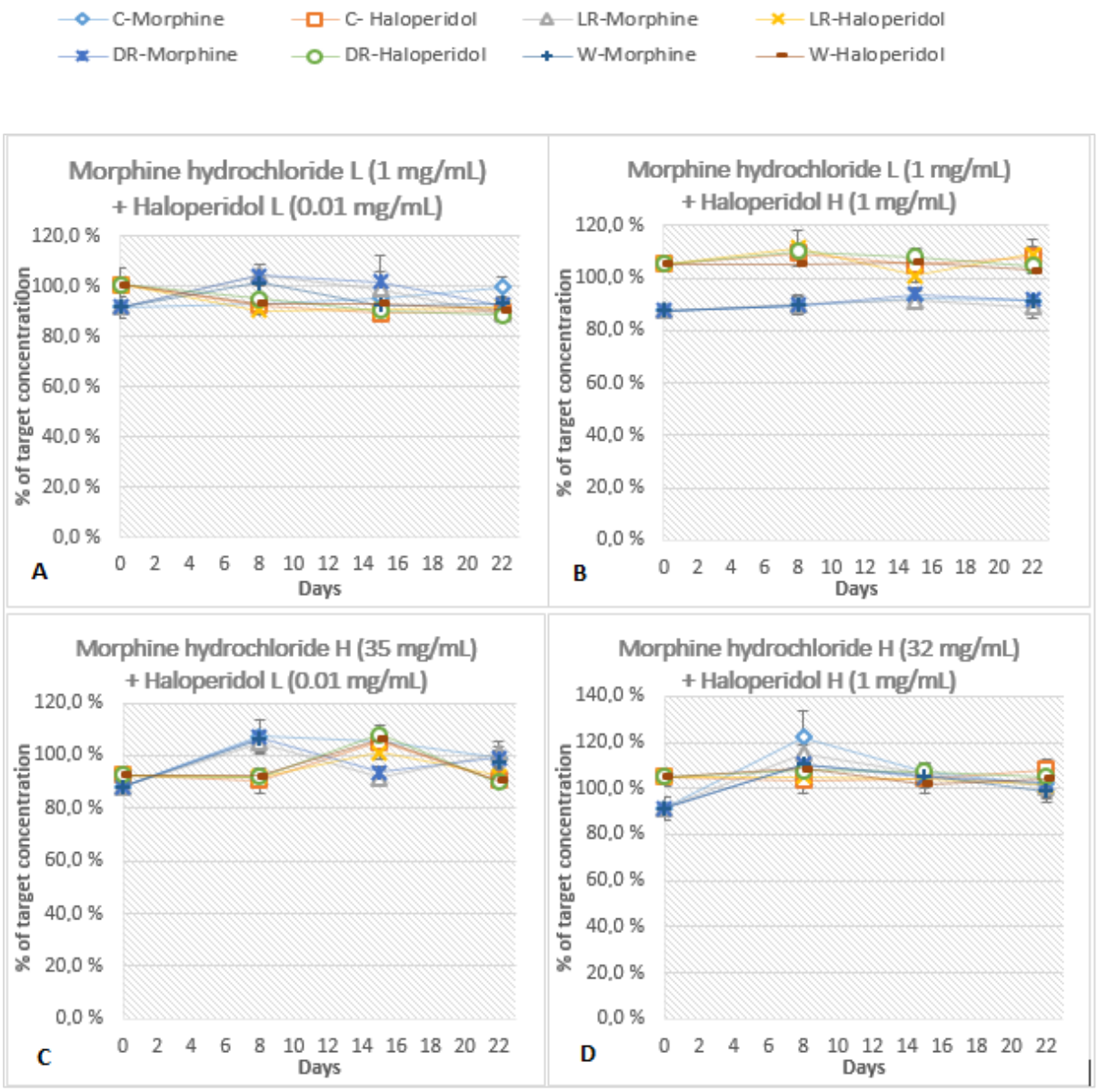

Figure 20 - Binary admixtures with morphine HCl and haloperidol

There was no change in colour, nor any precipitation in the vials after 22 days. Some white coating occurred around the rubber closure of the vials stored at 37 °C (**Figure 20 A, C and D**) shows some fluctuations in the concentration of both morphine and haloperidol.

Mor L + Hal H (**Figure 20 B**), however, seems overall stable through the whole storage time. In 15LR and 15DR, there were occasions where the morphine peaks in the chromatogram were right up to the injection signal, leading to discarding some of the values. Some uncertainty due to less data basis must therefore be expected.
In both Mor L + Hal L and H, exposure to light did not seem to have any great significance in loss of drug in these drug combinations.

Morphine HCl alone is, based on previous records, considered as stable for up to several months when diluted with 0.9 % NaCl as mentioned in section **5.2.1**, but few studies include morphine HCl and haloperidol. One study indicated that morphine HCl is compatible and stable with haloperidol for up to 28 days (47), and the loss was under 10 %.

5.4.2 Oxycodone HCl + haloperidol

See **Appendix II page K and L** for all average values.

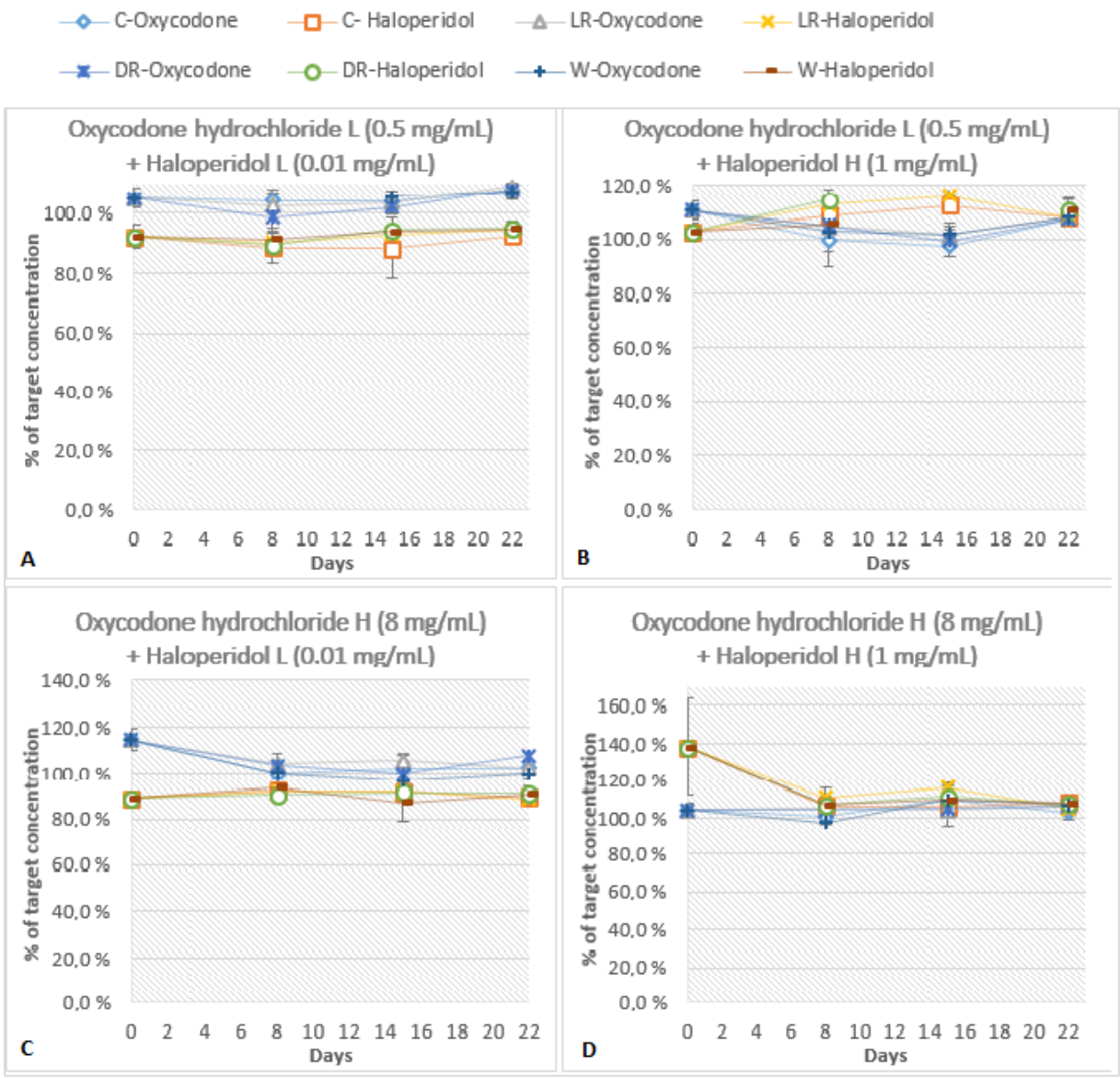

Figure 21 - Binary admixtures with oxycodone HCl and haloperidol

No colour changes were observed in 22 days for all combinations of oxycodone and haloperidol. Precipitation did also not occur. The only exception was the glass vial with day 22-C Oxy H + Hal L, where two tiny and white particles could barely be observed.

Figure 21 D of Oxy H + Hal H shows a very high initial value (137.9 %) with an extremely high standard deviation as well (25.8 %), which can be explained with the instrumentation. There were low read peak area of I.S. for most of the parallels while the peak areas of haloperidol were quite normal, compared to previous values for the other admixtures. The peak area of I.S. was about half to a third of the normal value.

5.4.3 Hydromorphone HCl + haloperidol

See **Appendix II page M and N** for all average values.

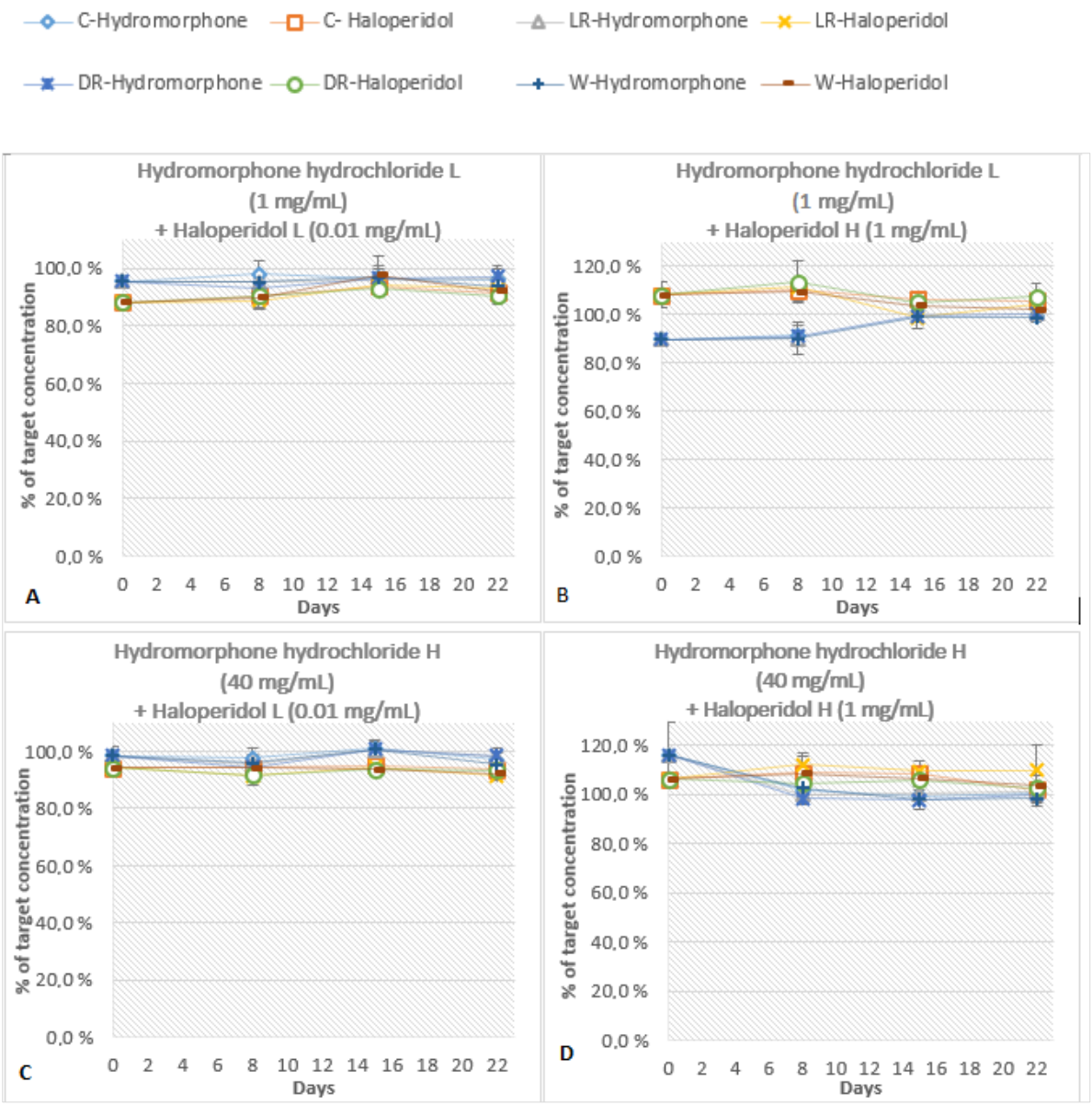

Figure 22 - Binary admixtures with hydromorphone HCl and haloperidol

No precipitation or change in colour was detected during 22 days. Hydromorphone in low and high concentration seems generally stable in combination with haloperidol in low concentration (**Figure 22 A and C**), but there is a small increase on day 15 for haloperidol in Mor L + Hal L. There is little or no loss after 22 days regardless of storage condition for both admixtures. Due to technical issues, the deviation for Hyd H + Hal H (**Figure 22 D**) is relatively high at day 0 (13,1 %). Then, after 8 days and further, the concentration of hydromorphone seems to stabilize at 100 %. As for all the other binary admixtures, uncertainty in the results is present and the experiments should be redone.

5.4.4 Morphine HCl + midazolam

See **Appendix II page O** for all average values.

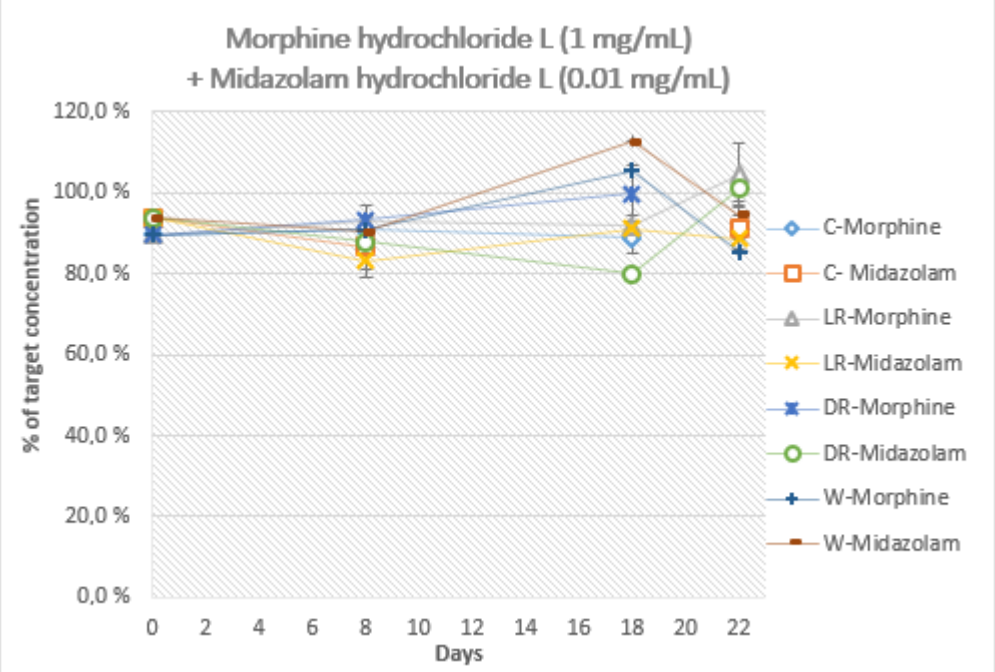

Figure 23 - Binary admixtures with morphine HCl and midazolam HCl, both low concentration

No colour change or precipitation occurred in 22 days.

A lot of fluctuations occurred during the storage period. Few values were readable due to split peaks of the I.S. in the chromatogram. The results on this admixture were poor in general, and the uncertainty in the values is very high.

Morphine HCL L + Midazolam HCl H day 15 and 22 were not analysed due to split peaks on the chromatogram, and all the peaks on day 8 did also have split peaks. In practice, there are no available data on this admixture except from day 0 and in not included.

The pH- value of the ammonium acetic- buffer (mobile phase A) was 7.4, which may have been too high, even though the peaks were quite acceptable at first. Midazolam is most stable at lower pH-values (48) and previous assays of midazolam have been operating with mobile phases with low pH around 3.5

5.4.5 Summary of the binary admixtures

The measured concentration of morphine, oxycodone and hydromorphone tend to decrease slightly more when the concentration of haloperidol is high, but it is not uniform.

So far for midazolam, it does not look particularly stable in the singular admixtures, nor binary admixtures with the current method which has already been discussed in section **5.2.5**.

In total, the trends in the results are unclear. Many of the results show that there are high uncertainties in the data, and because of this the data should not be used to put an eventual increased shelf life on the produced admixtures. The uncertain data is probably due to skill of the operator, especially pipetting technique. The admixtures with high concentration of morphine and haloperidol had to be diluted twice (**Table 9**), which in the worst case may contribute to additional error. There have also been challenges with the equipment and instrumentation (HPLC) for several days straight during the test period which most certainly have affected many of the results. It is nevertheless not clear what have affected the results the most. It could be either errors done by the operator, instrument issues or even a mix of both.

If the results in general are very uncertain, it may have little utility to describe and discuss all the single results in detail. It may be a good idea not to overestimate the results in an early stage, but rather continue with follow-up studies to support the obtained results, eventually.

However, the results are very important for the supply of new data on compatibility, which have been demonstrated with “extreme” variations in concentrations of binary admixtures with 0.9 % NaCl as diluent. It is not clearly visible in the data that any compounds do not tolerate increased storage.

5.5 Limitations

There were some limitations in the study, which should be considered in eventual further studies with another lab, another operator to show that the results are not lab or operator dependent.

The admixtures were not tested for antimicrobial contamination, as they were prepared aseptically using sterile drug solutions, diluents, glass containers and CADD® reservoirs. However, studies on oxycodone and hydromorphone in 0.9 % NaCl have been taking microbial assay into account, concluding that both admixtures are microbiologically stable after several weeks when prepared under aseptic conditions (21, 25).

0.9 % NaCl was the only diluent tested in this project, so 5 % glucose should also be tested for future studies.

Even though 3 replicates of each admixture dilution were made, they were made from just one glass vial or cassette. Eventual differences in the batches will therefore not be detected and there is a possible risk of incorrect results. The optimum would have been at least 3 vials from different batches on every storage condition with 3 replicates of each, but the duration of the HPLC analysis was the limiting factor in this project. A sample set run lasted for about 7.5 hours, so a threefold of increase of samples would have lasted too long. On the other hand, if only one storage or two storage conditions are to be tested, it is possible to increase the number of parallels.

5.6 Suggestions for further research

The possible combinations of several compounds and their concentrations in admixtures are almost endless. Rather "extreme" variation in concentrations (e.g. 40-fold from the lowest concentration of hydromorphone) have been studied in this project. Even though binary admixtures seem stable in both low and high concentrations, there is no guarantee that admixtures with concentrations in between the tested ones will be stable over a long period as well. Examples of binary admixtures with therapeutic concentrations should be tested in further research. E.g. for haloperidol, frequently used concentrations are from 0.1 mg/mL to 0.9 mg/mL. The highest concentration ever used for analgesic admixtures at the hospital pharmacy in Tromsø is 0.94 mg/mL (35).

The time interval for analysis have been every 1 week, and may be extended to every third or fourth day if possible for more certain determination of eventual degradation. Degradation products in the admixtures have not been identified in this project, and could be included in further stability studies. A higher temperature of 50 – 60 °C instead of 37 °C may be used to initiate forced degradation of the compounds.

The analytical method for admixtures containing midazolam need to be optimized, and a suggestion is to start initially with lowering the pH of the mobile phases to e.g. 3.5 or 4 instead of 7.4. Mobile phases with lower pH have been used before and could possibly give more accurate results, but it must be ensured that all the other compounds also go along with it.

In addition, assays of ternary admixtures in both glass vials and CADD® reservoirs are also highly required in the future due to little existing data and the frequent use of ternary analgesic admixtures in palliative medicine.

6 Conclusion

A rapid method which identifies morphine, hydromorphone, oxycodone and haloperidol in 6 minutes has been developed. Due to the uncertainty of the data, the method for midazolam should be modified, initially with lowering the pH of the mobile phases to e.g. 3.5 instead of 7.4. Binary admixtures with morphine and midazolam do not seem to be stable so far with the current method.

Admixtures containing morphine, oxycodone or hydromorphone (all as HCl salt) are all visually compatible with haloperidol, but should be stored in room temperature and protected from light to avoid precipitation, especially when the concentration of haloperidol is high. This have already been considered in current practice when mixing the analgesic admixtures directly into light protecting PCV cassettes.

Many of the results obtained are largely uncertain, and should be repeated with another operator and another laboratory/instrument to confirm the results. It is highly possible that many of the results in this project have been affected by errors done by the operator (pipetting) and/or instrumentation errors.

It is recommended that new stability studies will follow up this preliminary study, because of the high clinical relevance of this field the present day, but even more in the future.

References

1. Waters. How Does High Performance Liquid Chromatography Work? [cited 2017 10.01]. Available from: http://www.waters.com/waters/en_NO/How-Does-High-Performance-Liquid-Chromatography-Work%3F/nav.htm?cid=10049055&locale=en_NO.
2. Forrest WH, Jr., Smethurst PW, Kienitz ME. Self-administration of intravenous analgesics. Anesthesiology. 1970;33(3):363-5.
3. Sidebotham D, Dijkhuizen MRJ, Schug SA. The safety and utilization of patient-controlled analgesia. J Pain Symptom Manag. 1997;14(4):202-9.
4. Citron ML, Johnston-Early A, Boyer M, Krasnow SH, Hood M, Cohen MH. Patient-controlled analgesia for severe cancer pain. Arch Intern Med. 1986;146(4):734-6.
5. Swanson G, Smith J, Bulich R, New P, Shiffman R. Patient-Controlled Analgesia for Chronic Cancer Pain in the Ambulatory Setting - a Report of 117 Patients. J Clin Oncol. 1989;7(12):1903-8.
6. Stat. meld. no. 47: Samhandlingsreformen - Rett behandling - på rett sted - til rett tid. www.regjeringen.no: Ministry of Health and Care Sevices in Norway 2008.
7. Aulton ME. Aulton's Pharmaceutics - The Design and Manufacture of Medicines. 3rd ed: Churchill Livingstone; 2007.
8. 5.0 PE. Plastic Containers for Aqueous Solutions for Parenteral Infusion. 2005. In: European Pharmacopoeia 50 [Internet]. [309]. Available from: http://library.njucm.edu.cn/yaodian/ep/EP5.0/03_materials_and_containers/3.2._containers/3.2.2.1.%20Plastic%20containers%20for%20aqueous%20solutions%20for%20parenteral%20infusion.pdf.
9. Q1A: Stability testing of new active substances and medicinal products www.ich.org: International Conference of Harmonization (ICH); 1993 [updated 06.02.2003; cited 2017. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2__Guideline.pdf.
10. Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances www.ema.europa.eu: International Conference on Harmonization; 2000 [cited 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002823.pdf.
11. Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products www.ich.org: International Conference on Harmonization; 1996 [cited 2017. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1B/Step4/Q1B_Guideline.pdf.
12. UNN. Håndbok i lindrende behandling 2004 [Available from: https://unn.no/Documents/Kompetansetjenester,%20-sentre%20og%20fagr%C3%A5d/Regionalt%20kompetansesenter%20for%20lindrende%20behandling/handbok_lindrende_behandling_revidert_2016.pdf.
13. Yeh SY, Lach JL. Stability of morphine in aqueous solution. III. Kinetics of morphine degradation in aqueous solution. J Pharm Sci. 1961;50:35-42.

14. Yeh SY, Lach JL. Stability of morphine in aqueous solution. II. Separation of morphine from its degradation products. J Pharm Sci. 1961;50:30-4.
15. Vermeire A, Remon JP. Stability and compatibility of morphine. Int J Pharm. 1999;187(1):17-51.
16. Travell J. A contribution to the pharmacology of pseudomorphine. J Pharmacol Exp Ther. 1932;44(2):123-50.
17. Vermeire A, Remon JP. The solubility of morphine and the stability of concentrated morphine solutions in glass, polypropylene syringes and PVC containers. Int J Pharm. 1997;146(2):213-23.
18. PubChem. 2D Structure [04.14.17]. Data deposited in or computed by PubChem]. Available from: https://pubchem.ncbi.nlm.nih.gov.
19. Legemiddelverket. Summary of Product Characteristics for OxyNorm injection, 10 and 50 mg/ml [updated 08.02.2016. Available from: https://www.legemiddelsok.no/_layouts/15/Preparatomtaler/Spc/2002-00216.pdf
20. Turnbull K, Bielech M, Walker S. Stability of oxycodone hydrochloride for injection in dextrose and saline solutions. Can J Hosp Pharm. 2002;55:272-7.
21. Amri A, Ben Achour A, Chachaty E, Mercier L, Bourget P, Paci A. Microbiological and physicochemical stability of oxycodone hydrochloride solutions for patient-controlled delivery systems. J Pain Symptom Manage. 2010;40(1):87-94.
22. Gardiner P. Compatibility of an injectable oxycodone formulation with typical diluents, syringes, tubings, infusion bags and drugs for potential co-administration. Hosp Pharmacist. 2003;10:358-61.
23. Sarhill N, Walsh D, Nelson KA. Hydromorphone: pharmacology and clinical applications in cancer patients. Support Care Cancer. 2001;9(2):84-96.
24. Trissel LA, Xu QA, Pham L. Physical and Chemical Stability of Hydromorphone Hydrochloride 1.5 and 80 mg/mL Packaged in Plastic Syringes. Int J Pharm Compd. 2002;6(1):74-6.
25. Khondkar D, Chopra P, McArter JP, Rosen JA, Li SK. Chemical stability of hydromorphone hydrochloride in patient-controlled analgesia injector. Int J Pharm Compd. 2010;14(2):160-4.
26. Ensom MH, Decarie D, Leung K, Montgomery C. Stability of Hydromorphone-Ketamine Solutions in Glass Bottles, Plastic Syringes, and IV Bags for Pediatric Use. Can J Hosp Pharm. 2009;62(2):112-8.
27. Chandler SW, Trissel LA, Weinstein SM. Combined administration of opioids with selected drugs to manage pain and other cancer symptoms: initial safety screening for compatibility. J Pain Symptom Manage. 1996;12(3):168-71.
28. Walker S, Meinders A, Tailor H. Stability and compatibility of reconstituted sterile hydromorphone with midazolam. Can J Hosp Pharm. 1996;49:290-9.
29. Legemiddelverket. Summary of Proudct Characteristics, Palladon [updated 12.01.16. Available from: https://www.legemiddelsok.no/_layouts/15/Preparatomtaler/Spc/08-5879.pdf.
30. Andersin R, Tammilehto S. Photochemical Decomposition of Midazolam .4. Study of Ph-Dependent Stability by High-Performance Liquid-Chromatography. Int J Pharm. 1995;123(2):229-35.
31. Pramar YV, Loucas VA, el-Rachidi A. Stability of midazolam hydrochloride in syringes and i.v. fluids. Am J Health Syst Pharm. 1997;54(8):913-5.

32. Blaesel M, Peterson G, Jestrimski J, Kerry W. Stability of midazolam in sodium chloride infusion packs. J Pharm Pract Res. 1993;23(4):260-2.
33. Zeidler C, Dettmering D, Schrammel W, Spiteller M. Compatibility of various drugs used in intensive care medicine in polyethylene, PVC and glass infusion containers. Eur Hosp Pharm. 1999;5:106-10.
34. Forman JK, Souney PF. Visual compatibility of midazolam hydrochloride with common preoperative injectable medications. Am J Hosp Pharm. 1987;44(10):2298-9.
35. Ødegaard-Jensen EM. Personal communication. 2016.
36. Fraser GL, Riker RR. Visual Compatibility of Haloperidol Lactate with Injectable Solutions. Am J Hosp Pharm. 1994;51(7):905-6.
37. Schrijvers D, Tai-Apin C, De Smet MC, Cornil P, Vermorken JB, Bruyneel P. Determination of compatibility and stability of drugs used in palliative care. J Clin Pharm Ther. 1998;23(4):311-4.
38. Outman WR, Monolakis J. Visual Compatibility of Haloperidol Lactate with 0.9-Percent Sodium-Chloride Injection or Injectable Critical-Care Drugs during Simulated Y-Site Injection. Am J Hosp Pharm. 1991;48(7):1539-41.
39. Honoré Hansen S, Pedersen-Bjergaard S, Rasmussen K. Introduction to Pharmaceutical Chemical Analysis: John Wiley & Sons Ltd.; 2012.
40. Q2(R1): Validation of Analytical Procedures: Text and Methodology www.ich.org: International Conference on Harmonization; 1994 [updated 2005; cited 2017. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf.
41. Dixon WJ. Processing Data for Outliers. Biometrics. 1953;9(1):74-89.
42. Fawcett JP, Woods DJ, Munasiri B, Becket G. Compatibility of Cyclizine Lactate and Haloperidol Lactate. Am J Hosp Pharm. 1994;51(18):2292-.
43. Hecq JD, Godet M, Gillet P, Jamart J, Galanti L. Long-term stability of morphine hydrochloride in 0.9% NaCl infusion polyolefin bags after freeze-thaw treatment and in polypropylene syringes at 5 degrees C + 3 degrees C. Int J Pharm Compd. 2014;18(1):78-82.
44. Hagan RL, Jacobs LF, Pimsler M, Merritt GJ. Stability of Midazolam Hydrochloride in 5-Percent Dextrose Injection or 0.9-Percent Sodium-Chloride Injection over 30 Days. Am J Hosp Pharm. 1993;50(11):2379-81.
45. McMullin ST, Schaiff RA, Dietzen DJ. Stability of midazolam hydrochloride in polyvinyl chloride bags under fluorescent light. Am J Health Syst Pharm. 1995;52(18):2018-20.
46. Braun B. DEHP exposure [cited 2017 05.04]. Available from: http://www.safeinfusiontherapy.com/cps/rde/xchg/hc-safeinfusion-en-int/hs.xsl/15888.html.
47. Vermeire A, Remon JP. Compatibility and stability of morphine in binary admixtures with haloperidol, midazolam, dexamethasone or methylprednisolone. Int J Pharm. 1998;174(1–2):157-77.
48. Legemiddelverket. Summary of Product Characteristics, Midazolam [updated 12.05.14. Available from: https://www.legemiddelsok.no/_layouts/15/Preparatomtaler/Spc/06-4297.pdf.

Appendix I: Tables of results - singular admixtures

Morphine hydrochloride L (1 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + light	0	113.6 %	7.7 %
	8	109.9 %	2.6 %
	15	105.6 %	2.2 %
	22	104.8 %	2.9 %
Cold + dark	0	113.6 %	7.7 %
	8	107.2 %	1.1 %
	15	107.3 %	3.6 %
	22	107.8 %	2.9 %
Room temp. + light	0	113.6 %	7.7 %
	8	110.7 %	2.7 %
	15	108.6 %	2.9 %
	22	106.9 %	4.5 %
Room temp. + dark	0	113.6 %	7.7 %
	8	109.9 %	2.7 %
	15	104.9 %	1.4 %
	22	107.2 %	3.5 %
Warm + light	0	113.6 %	7.7 %
	8	103.7 %	1.3 %
	15	104.0 %	3.7 %
	22	105.5 %	1.9 %
Warm + dark	0	113.6 %	7.7 %
	8	104.1 %	5.0 %
	15	105.3 %	2.5 %
	22	105.4 %	2.0 %

Morphine hydrochloride L (1 mg/mL) in cassette

Day	% of target consentration, average	Std. dev.
0	92.1 %	2.4 %
8	90.5 %	3.0 %
15	107.4 %	0.0 %

Remarks: Due to technical issues, only 1 value was obtained at day 15, and no values on day 22.

Morphine hydrochloride H (35 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + light	0	102.4 %	0.3 %
	8	101.6 %	3.7 %
	15	102.4 %	4.0 %
	22	103.3 %	2.4 %
Cold + dark	0	102.4 %	0.3 %
	8	100.4 %	2.7 %
	15	107.9 %	1.2 %
	22	101.4 %	5.7 %
Room temp. + light	0	102.4 %	0.3 %
	8	105.2 %	3.1 %
	15	105.3 %	2.7 %
	22	105.0 %	2.7 %
Room temp. + dark	0	102.4 %	0.3 %
	8	104.4 %	4.7 %
	15	107.4 %	0.9 %
	22	109.6 %	3.3 %
Warm + light	0	102.4 %	0.3 %
	8	98.5 %	3.2 %
	15	102.1 %	1.5 %
	22	105.1 %	3.7 %
Warm + dark	0	102.4 %	0.3 %
	8	98.5 %	1.2 %
	15	105.1 %	3.7 %
	22	105.4 %	2.0 %

Morphine hydrochloride H (35 mg/mL) in cassette

Day	% of target consentration, average	Std. dev.
0	92.5 %	5.1 %
8	95.3 %	3.3 %
15	91.0 %	1.9 %

Remarks: Due to technical issues, no values were obtained at day 22.

Oxycodone hydrochloride L (0.5 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + light	0	115.9 %	4.6 %
	8	99.3 %	4.4 %
	15	107.5 %	7.3 %
	22	102.6 %	3.8 %
Cold + dark	0	115.9 %	4.6 %
	8	98.7 %	4.0 %
	15	105.5 %	2.5 %
	22	103.1 %	3.3 %
Room temp. + light	0	115.9 %	4.6 %
	8	104.3 %	4.1 %
	15	104.5 %	2.5 %
	22	108.7 %	2.1 %
Room temp. + dark	0	115.9 %	4.6 %
	8	110.4 %	4.3 %
	15	104.2 %	4.4 %
	22	105.1 %	3.3 %
Warm + light	0	115.9 %	4.6 %
	8	102.3 %	3.3 %
	15	102.3 %	3.8 %
	22	101.7 %	2.3 %
Warm + dark	0	115.9 %	4.6 %
	8	103.1 %	2.7 %
	15	108.8 %	7.6 %
	22	101.6 %	3.2 %

Oxycodone hydrochloride (0.5 mg/mL) in cassette

Day	% of target concentration, average	Std. dev.
0	102.7 %	3.1 %
8	103.8 %	3.4 %
15	106.8 %	3.4 %
22	108.5 %	2.4 %

Oxycodone hydrochloride H (8 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + light	0	100.9 %	4.6 %
	8	92.3 %	3.8 %
	15	108.8 %	4.9 %
	22	107.7 %	1.1 %
Cold + dark	0	100.9 %	4.6 %
	8	102.9 %	3.7 %
	15	107.9 %	3.6 %
	22	103.4 %	3.0 %
Room temp. + light	0	100.9 %	4.6 %
	8	100.3 %	2.0 %
	15	104.4 %	13.5 %
	22	107.0 %	3.5 %
Room temp. + dark	0	100.9 %	4.6 %
	8	100.0 %	2.2 %
	15	103.9 %	1.8 %
	22	102.4 %	2.0 %
Warm + light	0	100.9 %	4.6 %
	8	95.9 %	4.8 %
	15	101.7 %	2.5 %
	22	109.4 %	4.3 %
Warm + dark	0	100.9 %	4.6 %
	8	100.9 %	1.5 %
	15	102.0 %	3.8 %
	22	101.9 %	3.0 %

Oxycodone hydrochloride H (8 mg/mL) in cassette

Day	% of target concentration, average	Std. dev.
0	104.7 %	3.9 %
8	108.4 %	3.6 %
15	102.9 %	3.2 %
22	110.9 %	2.3 %

Hydromorphone hydrochloride L (1 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + light	0	106.8 %	6.8 %
	8	90.2 %	2.8 %
	15	100.7 %	4.5 %
	22	97.3 %	6.0 %
Cold + dark	0	106.8 %	6.8 %
	8	90.7 %	1.9 %
	15	103.7 %	4.3 %
	22	103.7 %	5.0 %
Room temp. + light	0	106.8 %	6.8 %
	8	95.5 %	2.8 %
	15	100.7 %	5.5 %
	22	103.5 %	4.3 %
Room temp. + dark	0	106.8 %	6.8 %
	8	96.5 %	6.7 %
	15	98.4 %	4.2 %
	22	100.8 %	5.2 %
Warm + light	0	106.8 %	6.8 %
	8	91.9 %	3.9 %
	15	99.2 %	5.0 %
	22	98.3 %	3.8 %
Warm + dark	0	106.8 %	6.8 %
	8	93.4 %	4.2 %
	15	96.7 %	5.7 %
	22	99.7 %	4.2 %

Hydromorphone hydrochloride L (1 mg/mL) in cassette

Day	% of target concentration	Std. dev.
0	99.7 %	3.2 %
8	99.6 %	4.8 %
15	98.1 %	4.2 %
22	100.1 %	6.1 %

Hydromorphone hydrochloride H (40 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + light	0	100.0 %	8.3 %
	8	88.0 %	3.8 %
	15	91.4 %	2.6 %
	22	88.8 %	7.4 %
Cold + dark	0	100.0 %	8.3 %
	8	92.9 %	3.9 %
	15	90.9 %	5.9 %
	22	85.5 %	3.6 %
Room temp. + light	0	100.0 %	8.3 %
	8	97.2 %	7.8 %
	15	90.0 %	3.6 %
	22	91.4 %	2.4 %
Room temp. + dark	0	100.0 %	8.3 %
	8	90.6 %	5.2 %
	15	92.9 %	2.7 %
	22	92.3 %	3.0 %
Warm + light	0	100.0 %	8.3 %
	8	93.7 %	4.2 %
	15	91.2 %	6.7 %
	22	88.5 %	5.1 %
Warm + dark	0	100.0 %	8.3 %
	8	91.7 %	6.4 %
	15	87.7 %	5.6 %
	22	89.7 %	3.7 %

Haloperidol L (0.01 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + light	0	137.5 %	3.0 %
	8	139.7 %	4.5 %
	15	133.2 %	3.7 %
	22	132.2 %	1.7 %
Cold + dark	0	137.5 %	3.0 %
	8	139.4 %	5.9 %
	15	133.1 %	2.1 %
	22	131.0 %	4.2 %
Room temp. + light	0	137.5 %	3.0 %
	8	139.0 %	5.6 %
	15	135.3 %	3.2 %
	22	136.6 %	6.3 %
Room temp. + dark	0	137.5 %	3.0 %
	8	133.4 %	5.7 %
	15	135.2 %	3.7 %
	22	132.7 %	3.8 %
Warm + dark	0	137.5 %	3.0 %
	8	131.1 %	3.2 %
	15	133.4 %	5.7 %
	22	129.4 %	2.8 %

Haloperidol H (1 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + dark	0	73.8 %	1.7 %
	8	129.9 %	4.4 %
	15	125.9 %	6.9 %
	22	32.2 %	0.5 %
Room temp. + light	0	73.8 %	1.7 %
	8	129.6 %	8.9 %
	15	113.7 %	2.2 %
	22	120.2 %	3.0 %
Room temp. + dark	0	73.8 %	1.7 %
	8	123.5 %	3.2 %
	15	120.0 %	2.7 %
	22	119.0 %	5.8 %
Warm + dark	0	73.8 %	1.7 %
	8	124.6 %	3.3 %
	15	122.0 %	4.3 %
	22	126.1 %	6.1 %

Midazolam L (0.01 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + dark	0	93.9 %	3.4 %
	8	90.9 %	2.4 %
	15	96.2 %	4.2 %
	22	100.5 %	3.3 %
Room temp. + light	0	93.9 %	3.4 %
	8	87.3 %	6.5 %
	15	92.7 %	5.6 %
	22	75.6 %	5.7 %
Room temp. + dark	0	93.9 %	3.4 %
	8	95.4 %	4.1 %
	15	95.2 %	3.0 %
	22	95.0 %	6.1 %
Warm + dark	0	93.9 %	3.4 %
	8	91.6 %	7.8 %
	15	90.6 %	2.7 %
	22	92.1 %	5.7 %

Remarks: Due to technical issues, only 3 values were obtained on room temp + light on day 22.

Midazolam H (4 mg/mL)

Storage condition	Day	% of target concentration	Std. dev.
Cold + dark	0	113.4 %	2.2 %
	8	79.6 %	5.7 %
	15	92.1 %	4.4 %
	22	85.0 %	11.1 %
Room temp. + light	0	113.4 %	2.2 %
	8	86.1 %	9.0 %
	15	91.6 %	9.6 %
	22	75.6 %	5.7 %
Room temp. + dark	0	113.4 %	2.2 %
	8	94.1 %	5.0 %
	15	93.9 %	2.7 %
	22	86.7 %	7.1 %
Warm + dark	0	113.4 %	2.2 %
	8	90.6 %	9.3 %
	15	85.5 %	0.0 %
	22	81.1 %	4.7 %

Remarks: Due to technical issues, only the following values were obtained:

- 15DR (n=3) + 22DR (n=4)
- 15W (n=1) + 22W (n=4)

Appendix II: Tables of results – binary admixtures

Morphine HCl L	**1 mg/mL**			
Haloperidol L	**0.01 mg/mL**			
Storage condition	**Day**	**Average Mor**	**Average Hal**	**Std.dev Mor**	**Std.dev Hal**
Cold	0	91.6 %	100.5 %	4.1 %	6.6 %
	8	92.8 %	92.3 %	1.6 %	2.0 %
	15	95.2 %	89.2 %	1.9 %	2.3 %
	22	99.5 %	90.0 %	2.1 %	1.2 %
Room temp. + light	0	91.6 %	100.5 %	4.1 %	6.6 %
	8	104.6 %	90.4 %	4.2 %	1.5 %
	15	98.8 %	90.7 %	7.0 %	3.0 %
	22	88.7 %	91.9 %	2.3 %	1.8 %
Room temp. + dark	0	91.6 %	100.5 %	4.1 %	6.6 %
	8	104.1 %	95.1 %	1.5 %	5.7 %
	15	101.8 %	90.4 %	10.7 %	1.1 %
	22	92.4 %	88.7 %	2.9 %	2.1 %
Warm	0	91.6 %	100.5 %	4.1 %	6.6 %
	8	101.3 %	93.1 %	7.7 %	2.7 %
	15	92.4 %	93.1 %	3.2 %	3.9 %
	22	93.2 %	90.5 %	2.6 %	1.4 %

Morphine HCl L	**1 mg/mL**				
Haloperidol H	**1 mg/mL**				
Storage condition	**Day**	**Morphine, average**	**Haloperidol, average**	**Std. dev morphine**	**Std. dev haloperidol**
Cold	0	87.6 %	105.3 %	0.9 %	2.1 %
	8	89.6 %	109.5 %	3.4 %	2.2 %
	15	92.0 %	105.1 %	3.8 %	6.4 %
	22	91.3 %	108.3 %	1.6 %	3.9 %
Room temp. + light	0	87.6 %	105.3 %	0.9 %	2.1 %
	8	90.0 %	111.4 %	2.6 %	6.7 %
	15	91.5 %	101.0 %	3.5 %	2.5 %
	22	88.8 %	109.1 %	4.0 %	5.6 %
Room temp. + dark	0	87.6 %	105.3 %	0.9 %	2.1 %
	8	89.8 %	110.1 %	4.1 %	1.7 %
	15	93.7 %	108.0 %	2.8 %	2.5 %
	22	91.8 %	104.7 %	1.5 %	3.2 %
Warm	0	87.6 %	105.3 %	0.9 %	2.1 %
	8	89.8 %	105.4 %	3.0 %	4.6 %
	15		106.1 %	0.0 %	3.6 %
	22	91.1 %	103.0 %	2.2 %	1.5 %

Remarks: Due to technical issues, no data obtained (black field).

Morphine HCl H	**35 mg/mL**			
Haloperidol L	**0.01 mg/mL**			
Storage condition	**Day**	**Average Mor**	**Average Hal**	**Std. dev Mor**	**Std. dev Hal**
Cold	0	88.0 %	92.8 %	2.9 %	2.0 %
	8	107.1 %	90.5 %	6.8 %	4.7 %
	15	105.7 %	105.1 %	3.9 %	6.4 %
	22	99.1 %	90.5 %	2.4 %	2.9 %
Room temp. + light	0	88.0 %	92.8 %	2.9 %	2.0 %
	8	105.0 %	91.8 %	3.5 %	2.8 %
	15	91.6 %	101.2 %	2.8 %	2.4 %
	22	100.6 %	92.1 %	4.7 %	2.9 %
Room temp. + dark	0	88.0 %	92.8 %	2.9 %	2.0 %
	8	107.0 %	92.0 %	2.8 %	3.7 %
	15	93.6 %	108.0 %	2.1 %	2.5 %
	22	99.0 %	90.0 %	4.6 %	1.7 %
Warm	0	88.0 %	92.8 %	2.9 %	2.0 %
	8	106.3 %	92.3 %	2.6 %	2.9 %
	15	[redacted]	106.1 %	[redacted]	3.6 %
	22	97.7 %	90.6 %	4.6 %	3.0 %

Remarks: Due to technical problems, no data obtained in the marked black fields.

Morphine HCl H	**32 mg/mL**			
Haloperidol H	**1 mg/mL**			
Storage condition	**Day**	**Average Mor**	**Average Hal**	**Std. dev Mor**	**Std. dev Hal**
Cold	0	91.3 %	105.1 %	4.9 %	4.0 %
	8	122.1 %	103.6 %	11.4 %	5.8 %
	15	107.0 %	104.1 %	3.8 %	6.0 %
	22	102.0 %	108.1 %	5.5 %	4.3 %
Room temp. + light	0	91.3 %	105.1 %	4.9 %	4.0 %
	8	115.1 %	105.2 %	3.9 %	2.4 %
	15	106.5 %	104.2 %	3.1 %	2.4 %
	22	100.9 %	101.7 %	6.6 %	2.2 %
Room temp. + dark	0	91.3 %	105.1 %	4.9 %	4.0 %
	8	110.4 %	107.6 %	4.7 %	3.9 %
	15	104.6 %	107.3 %	2.9 %	3.8 %
	22	102.1 %	105.1 %	4.0 %	2.9 %
Warm	0	91.3 %	105.1 %	4.9 %	4.0 %
	8	110.7 %	108.4 %	3.0 %	3.3 %
	15	105.4 %	101.9 %	2.1 %	1.9 %
	22	98.9 %	104.3 %	3.1 %	1.7 %

Oxycodone HCl L	**0.5 mg/mL**				
Haloperidol L	**0.01 mg/mL**				
Storage condition	**Day**	**Average Oxy**	**Average Hal**	**Std.dev Oxy**	**Std.dev Hal**
Cold	0	105.0 %	92.1 %	3.1 %	3.8 %
	8	103.9 %	88.4 %	3.8 %	5.1 %
	15	103.8 %	88.2 %	1.4 %	10.2 %
	22	107.3 %	92.4 %	2.1 %	0.0 %
Room temp. + light	0	105.0 %	92.1 %	3.1 %	3.8 %
	8	102.3 %	90.1 %	2.2 %	3.5 %
	15	103.5 %	93.0 %	3.9 %	1.5 %
	22	108.9 %	94.3 %	2.4 %	2.0 %
Room temp. + dark	0	105.0 %	92.1 %	3.1 %	3.8 %
	8	98.4 %	89.4 %	8.1 %	1.6 %
	15	101.8 %	94.4 %	1.6 %	0.7 %
	22	107.8 %	94.9 %	1.2 %	2.3 %
Warm	0	105.0 %	92.1 %	3.1 %	3.8 %
	8		91.3 %		3.8 %
	15	105.4 %	93.6 %	2.0 %	2.2 %
	22	107.1 %	94.7 %	2.8 %	1.8 %

Remarks: Due to technical issues, only one value obtained for haloperidol stored in dark at day 22, and no data obtained in the marked black fields.

Oxycodone HCl L	**0.5 mg/mL**				
Haloperidol H	**1 mg/mL**				
Storage condition	**Day**	**Average Oxy**	**Average Hal**	**Std.dev Oxy**	**Std.dev Hal**
Cold	0	110.5 %	102.8 %	3.3 %	3.1 %
	8	99.7 %	108.7 %	9.5 %	2.4 %
	15	97.5 %	112.2 %	3.8 %	0.0 %
	22	107.4 %	108.0 %	0.8 %	2.2 %
Room temp. + light	0	110.5 %	102.8 %	3.3 %	3.1 %
	8	104.7 %	112.7 %	2.0 %	2.3 %
	15	101.4 %	116.1 %	4.9 %	0.0 %
	22	108.1 %	107.9 %	2.0 %	3.1 %
Room temp. + dark	0	110.5 %	102.8 %	3.3 %	3.1 %
	8	105.0 %	114.4 %	4.9 %	3.7 %
	15	99.3 %		5.3 %	
	22	107.4 %	110.8 %	2.0 %	4.1 %
Warm	0	110.5 %	102.8 %	3.3 %	3.1 %
	8	102.7 %	105.5 %	2.1 %	9.8 %
	15	101.7 %		2.1 %	
	22	108.0 %	110.5 %	1.7 %	3.9 %

Remarks: No available data due to technical issues are marked in black.

Oxycodone HCl H		**8 mg/mL**			
Haloperidol L		**0.01 mg/mL**			
Storage condition	**Day**	**Average Oxy**	**Average Hal**	**Std.dev Oxy**	**Std.dev Hal**
Cold	0	114.6 %	88.9 %	4.9 %	3.2 %
	8	99.6 %	92.1 %	4.6 %	2.2 %
	15	101.9 %	91.8 %	6.6 %	3.9 %
	22	102.2 %	89.3 %	2.8 %	1.8 %
Room temp. + light	0	114.6 %	88.9 %	4.9 %	3.2 %
	8	104.0 %	91.9 %	4.4 %	2.9 %
	15	105.5 %	91.9 %	2.2 %	2.6 %
	22	102.1 %	88.6 %	2.6 %	2.5 %
Room temp. + dark	0	114.6 %	88.9 %	4.9 %	3.2 %
	8	103.2 %	90.3 %	2.8 %	2.1 %
	15	99.6 %	91.5 %	3.3 %	2.5 %
	22	107.5 %	91.0 %	1.6 %	3.3 %
Warm	0	114.6 %	88.9 %	4.9 %	3.2 %
	8	100.1 %	93.8 %	3.1 %	3.6 %
	15	97.0 %	87.0 %	8.1 %	8.0 %
	22	99.9 %	90.8 %	2.2 %	2.0 %

Remarks:

Oxycodone HCl H		**8 mg/mL**			
Haloperidol H		**1 mg/mL**			
Storage condition	**Day**	**Average Oxy**	**Average Hal**	**Std.dev Oxy**	**Std.dev Hal**
Cold	0	104.3 %	137.9 %	3.8 %	25.8 %
	8	100.4 %	106.2 %	3.8 %	3.7 %
	15	109.5 %	105.9 %	2.8 %	10.7 %
	22	102.6 %	108.1 %	3.9 %	3.4 %
Room temp. + light	0	104.3 %	137.9 %	3.8 %	25.8 %
	8	105.7 %	110.8 %	2.4 %	5.1 %
	15	104.1 %	116.1 %	3.5 %	2.5 %
	22	106.1 %	104.9 %	2.3 %	1.5 %
Room temp. + dark	0	104.3 %	137.9 %	3.8 %	25.8 %
	8	103.9 %	106.7 %	4.2 %	4.6 %
	15	105.0 %	111.2 %	1.9 %	6.3 %
	22	106.5 %	107.2 %	3.3 %	3.4 %
Warm	0	104.3 %	137.9 %	3.8 %	25.8 %
	8	97.4 %	106.6 %	4.2 %	2.8 %
	15	109.4 %	109.4 %	5.9 %	5.7 %
	22	106.9 %	107.6 %	2.1 %	4.1 %

Hydromorphone HCl L **1 mg/mL**
Haloperidol L **0.01 mg/mL**

Storage condition	Day	Average Hyd	Average Hal	Std.dev Hyd	Std.dev Hal
Cold	0	95.4 %	88.2 %	1.6 %	2.1 %
	8	98.1 %	90.3 %	4.7 %	4.3 %
	15	96.5 %	93.6 %	4.2 %	0.3 %
	22	96.0 %	91.5 %	2.9 %	3.0 %
Room temp. + light	0	95.4 %	88.2 %	1.6 %	2.1 %
	8	95.0 %	88.7 %	2.3 %	2.8 %
	15	95.7 %	94.0 %	2.0 %	1.4 %
	22	96.3 %	92.8 %	2.1 %	2.2 %
Room temp. + dark	0	95.4 %	88.2 %	1.6 %	2.1 %
	8	93.2 %	90.5 %	1.8 %	3.9 %
	15	96.4 %	92.9 %	3.2 %	1.2 %
	22	97.1 %	90.3 %	4.1 %	1.9 %
Warm	0	95.4 %	88.2 %	1.6 %	2.1 %
	8	95.2 %	89.8 %	1.5 %	3.5 %
	15	96.8 %	97.7 %	2.1 %	6.7 %
	22	93.8 %	92.0 %	6.0 %	4.5 %

Hydromorphone HCl L **1 mg/mL**
Haloperidol H **1 mg/mL**

Storage condition	Day	Average Hyd	Average Hal	Std.dev Hyd	Std.dev Hal
Cold	0	89.7 %	108.1 %	2.2 %	5.3 %
	8	91.4 %	110.0 %	2.5 %	3.9 %
	15		106.6 %		2.3 %
	22	99.5 %	105.7 %	1.6 %	7.0 %
Room temp. + light	0	89.7 %	108.1 %	2.2 %	5.3 %
	8	90.2 %	111.4 %	6.9 %	3.7 %
	15		98.7 %		4.6 %
	22	100.8 %	104.3 %	3.6 %	3.2 %
Room temp. + dark	0	89.7 %	108.1 %	2.2 %	5.3 %
	8	91.1 %	113.6 %	4.3 %	8.9 %
	15	99.5 %	105.2 %	2.5 %	2.3 %
	22	100.3 %	107.3 %	2.7 %	0.1 %
Warm	0	89.7 %	108.1 %	2.2 %	5.3 %
	8	90.2 %	109.5 %	2.3 %	4.1 %
	15	99.1 %	103.7 %	2.3 %	1.4 %
	22	98.7 %	102.2 %	1.5 %	3.1 %

Remarks: No values obtained in the black fields due to technical issues.

Hydromorphone HCl H 40 mg/mL
Haloperidol L 0.01 mg/mL

Storage condition	Day	Average Hyd	Average Hal	Std.dev Hyd	Std.dev Hal
Cold	0	98.5 %	94.3 %	3.3 %	1.5 %
	8	97.6 %	94.1 %	3.7 %	2.3 %
	15	101.1 %	95.0 %	2.2 %	2.6 %
	22	97.2 %	93.8 %	2.3 %	1.4 %
Room temp. + light	0	98.5 %	94.3 %	3.3 %	1.5 %
	8	95.5 %	91.4 %	3.5 %	1.8 %
	15	100.5 %	94.4 %	3.4 %	1.7 %
	22	98.1 %	91.3 %	3.0 %	1.2 %
Room temp. + dark	0	98.5 %	94.3 %	3.3 %	1.5 %
	8	94.4 %	91.6 %	3.7 %	3.7 %
	15	100.6 %	93.8 %	3.4 %	1.2 %
	22	98.4 %	93.3 %	1.4 %	2.0 %
Warm	0	98.5 %	94.3 %	3.3 %	1.5 %
	8	95.8 %	94.2 %	2.0 %	5.2 %
	15	100.7 %	93.8 %	3.4 %	2.0 %
	22	95.3 %	92.1 %	4.3 %	3.2 %

Hydromorphone HCl H 40 mg/mL
Haloperidol H 1 mg/mL

Storage condition	Day	Average Hyd	Average Hal	Std.dev Hyd	Std.dev Hal
Cold	0	116.1 %	106.1 %	13.1 %	2.5 %
	8	101.7 %	108.7 %	3.4 %	2.6 %
	15	99.3 %	108.6 %	1.5 %	2.3 %
	22	100.3 %	102.0 %	3.4 %	2.7 %
Room temp. + light	0	116.1 %	106.1 %	13.1 %	2.5 %
	8	100.1 %	112.2 %	3.3 %	4.7 %
	15	100.4 %	109.6 %	3.1 %	4.2 %
	22	101.4 %	110.0 %	3.1 %	9.8 %
Room temp. + dark	0	116.1 %	106.1 %	13.1 %	2.5 %
	8	98.3 %	104.4 %	2.4 %	4.0 %
	15	97.7 %	105.8 %	2.1 %	2.0 %
	22	100.1 %	102.7 %	3.7 %	3.4 %
Warm	0	116.1 %	106.1 %	13.1 %	2.5 %
	8	102.5 %	108.4 %	5.6 %	7.2 %
	15	97.8 %	106.5 %	4.2 %	3.5 %
	22	98.3 %	103.5 %	3.4 %	4.4 %

Morphine HCl L		**1 mg/mL**			
Midazolam HCl L		**0.01 mg/mL**			
Storage condition	**Day**	**Average Mor**	**Average Mid**	**Std.dev Mor**	**Std.dev Mid**
Cold	0	89.7 %	93.8 %	1.4 %	1.6 %
	8	90.9 %	86.7 %	2.9 %	7.7 %
	18	89.0 %		4.2 %	
	22		91.3 %		5.2 %
Room temp. + light	0	89.7 %	93.8 %	1.4 %	1.6 %
	8	92.9 %	83.3 %	4.0 %	4.0 %
	18	91.9 %	91.2 %	2.4 %	0.0 %
	22	104.5 %	88.6 %	7.7 %	0.0 %
Room temp. + dark	0	89.7 %	93.8 %	1.4 %	1.6 %
	8	93.2 %	88.0 %	1.3 %	6.7 %
	18	99.9 %	80.0 %	7.0 %	0.0 %
	22		100.9 %		2.8 %
Warm	0	89.7 %	93.8 %	1.4 %	1.6 %
	8	90.8 %	90.5 %	0.0 %	1.2 %
	18	105.5 %	112.7 %	0.0 %	0.0 %
	22	85.5 %	94.5 %	0.0 %	0.0 %

Remarks: No data obtained in the black fields due to technical issues.

Appendix III – working sheet template

Masteroppgave 2016/2017 SYKEHUSAPOTEK NORD DAVVI BUOHCCEVIESSOAPOTEHKA	Versjon/dato 18.04.2017	Mengde 20 x 5 ml	Beregninger kontrollert	
	Prod.nr.			
	Vask før prod.	Arb.sone klargjort	Vask etter prod.	Prod.dato

Innholdsstoffer:	Mengde	Batchnr.	Holdbarhet	Sign
Natriumklorid ''Fresenius''	100,0 ml			

Prosedyre	Prosedyrekontroll	Sign
#I/T	Aseptisk arbeidsteknikk Visuell kontroll av produkt	

Emballasje	Antall	Syklusnr. sterilisering	Dato sterilisert	Sign
Injeksjonsglass 100 ml	1			
Injeksjonsglass 10 ml	18			
Propp til injeksjonsglass, gummi	19			
Hette t/inj glass (ikke avrivbar)	19			
Injeksjonsglasskartong 10 ml	9			

A-regnskap				
Legemiddel	Mengde	Tatt ut (sign)	Satt inn (sign)	Kassasjon rest produksjon
	###			Rester A-preparater kassert: /
	###			
	###			
	###			

Etikett	Anmerkninger

Kassasjon endt analyse	Antall	Dato	Sign			
Hetteglass utlevert	19 hgl		/			
Hetteglass tilbakelevert og kassert	*Test d0* 1 hgl		/	*Test d8* 3 hgl		/
	Test d15 3 hgl		/	*Test d22* 3 hgl		/