Formulation and Stability of Extemporaneously Prepared Morphine Oral Suspension

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ABSTRACT

Morphine taken by mouth is an effective analgesic for most people with moderate or severe cancer pain. Hospital pharmacists commonly prepare morphine oral liquid extemporaneously for cancer patients who require tube feeding or have difficulties in swallowing because it is not available commercially in Malaysia. This study aims to provide the physical, chemical and microbiological stability data to determine the shelf-life and storage condition for the extemporaneous preparation of morphine oral suspension (10mg/5ml) using X-Temp Oral Suspension System. The samples were divided into 2 groups and were stored at 4ºC (refrigeration) and 30ºC / 75%RH (room temperature) protected from light for 12 months. The physical, chemical and microbiological stability were examined at the interval of months 0, 1, 2, 3, 4, 5, 6, 9 and 12. The content of morphine was determined using HPLC-UV method. The content of morphine remained above 95% of the original concentration throughout the study period. The colour, clarity and odour remained fairly unchanged throughout the study period and the pH values were steady at around pH 4. The extemporaneous preparation was not susceptible to microbial contamination. The results from the stability studies confirmed that the new formulation of morphine oral suspension is stable for up to 12 months when packed in HDPE bottles with polypropylene caps and stored at both 4ºC and 30ºC / 75%RH.

INTRODUCTION

Morphine is an opioid analgesic used to relieve severe, acute pain or moderate to severe, chronic pain for patients with cancer, myocardial infarction and surgery (1,2). Morphine taken by mouth is an effective analgesic for cancer pain and is considered the drug of first choice for relieving moderate to severe pain (3). Moderate to severe pain in cancer is common and affects 70 to 80% of patients with advanced disease (3). Morphine has remained the first choice for reasons of familiarity, availability and cost rather than proven superiority (3).

According to the World Health Organization (WHO), morphine is given orally as an aqueous morphine solution or as standard immediate-release tablet every four hours by the clock (4). Modified-release tablets or capsules are available in both 12 hour and 24 hour release patterns and should be swallowed whole (5). The effective dose may vary from as little as 5mg to more than 1000mg partly because of individual variations in systemic bioavailability (4). Immediate-release formulations (tablet or aqueous solution) are much more flexible than long-acting preparations, both in the dose titration period and when the pain is poorly controlled (3). When compared to immediate- and modified-release morphine tablets, morphine oral solution has an earlier onset and is easier to take and more convenient for dose titration (6).

The lack of commercially available oral liquid dosage form is an on-going problem for health care providers in many practice settings. The pharmacist, both in community and hospital pharmacy practice, is often challenged with the preparation of a liquid dosage form not available for paediatric

patients, those adults unable to swallow tablets or capsules and patients who must receive medications via nasogastric or gastrostomy tubes (7).

When there is a need to undertake extemporaneous preparation, the accountable pharmacist must choose a validated formula with supporting stability data (8,9). However, when the stability data and validated formulations are not available, further research should be carried out to validate the formulations used in practice whenever possible and then the formulations should be standardized among all the hospitals (9).

Morphine oral liquid is preferred in cancer patients who require tube feeding or have difficulties in swallowing (6). Many hospital pharmacists have to prepare morphine oral liquid extemporaneously because it is not available commercially (9). In Malaysia, pharmacists in major hospital are tasked to prepare morphine oral liquids on a weekly basis to supply them to outpatient departments, satellite pharmacies and wards. Therefore, it is ideal that the morphine oral liquid has longer shelf-life to meet the clinical requirements of the outpatients who are taking this medicine and also to minimize wastage due to short expiry.

Extemporaneous preparation remains one of the highest risks preparative activities carried out in the pharmacy, as the risks of unlicensed medicines are combined with inherent risks associated with the pharmaceutical compounding process (8). Formulation failure can occur when a formulation has not been adequately validated, potentially resulting in either under- or overdose and associated toxicity or therapeutic failure (8). The causes of formulation failure are numerous and can be complex, including physical incompatibilities, drug/excipient binding issue and drug degradation (8). Generally, as the complexity of the formulation increases so does the risk of problems occurring. Therefore, the formulation of the extemporaneous preparation should be designed as simple as possible for these reasons (8).

According to the USP36-NF31 Chapter <795>, Pharmaceutical Compounding – Nonsterile Preparations (10), an extemporaneous oral liquid has a beyond-use date (BUD) of not more than 14 days shelf-life when stored at controlled cold temperatures if no stability information or supporting data is available. This study will provide the stability data needed to determine the shelf-life and storage condition for the extemporaneous preparation of morphine oral liquid. The results from the stability studies are important to validate the formulation and to confirm that the extemporaneous preparation remains stable and efficacious during the course of their use.

An oral formulation can be prepared from morphine sulfate or hydrochloride salt (4,5). Morphine hydrochloride is a colourless, white or almost white, crystalline powder. It is efflorescent in a dry atmosphere. It is soluble in water, slightly soluble in alcohol and practically insoluble in toluene (2).

Oral liquids are usually formulated as either a suspension or solution. Drugs in solution are more susceptible to chemical degradation than drugs in the solid state and this should be considered when preparing a solution (11). Extemporaneous preparation made from tablets contains excipients such as binders and disintegrating agents in addition to the active drug. Insoluble tablet excipients may compromise the product appearance of the suspension whereas soluble tablet excipients may reduce drug stability, for example, by altering the pH of the preparation (11).

When considering the suitability of an extemporaneous oral liquid, a number of factors, in addition to chemical stability of active pharmaceutical ingredient (API) need to be considered. This includes physical stability, microbial stability, palatability, excipient suitability (e.g. sugar free for diabetic patients), interactions with packaging materials, accurate compounding procedures including calculations and cost (12).

Since sourcing of API for morphine hydrochloride is possible, pure drug substance is preferred over commercially available tablet for compounding of oral liquids. The use of commercially available suspending base is encouraged and is considered an excellent choice for making the extemporaneous

preparations as simple for the inexperienced pharmacist making one-off preparations (13). Commercial vehicles are considered a convenient choice since many practice settings may not stock a wide variety of excipients and many of the stability studies in the literature on oral liquids prepared extemporaneously utilize these commercial vehicles (12).

MATERIALS AND METHODS

Formulation and Study Design

The extemporaneous preparation of morphine oral suspension (10mg/5ml) was prepared by the pharmacy department of Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The API of morphine hydrochloride BP, PhEur. was sourced from Johnson Matthey / Macfarlan Smith Limited, United Kingdom and the commercial vehicle, X-Temp Oral Suspension System was supplied by Pharm-D Sdn Bhd, Malaysia (**Figure 1**).

Figure 1: Master formula for morphine oral suspension

Ingredient	Amount
Morphine HCl Powder	10g
X-Temp Oral Suspension System	qs ad 5000ml

The commercial vehicle chosen contains specialized suspending system formulated to assist in extemporaneous preparation of oral liquid, non-soluble (suspended), aqueous dosage form and is an orange flavoured, sweetened, sugar-free vehicle containing suitable preservatives. The morphine oral suspension was packed into 100ml semi-transparent high-density polyethylene (HDPE) bottles and was fitted with white polypropylene screw caps.

Fifty-five bottles of morphine oral suspension were divided into 2 groups and one group was stored at 4 ± 2ºC (refrigeration) and the other was stored at 30 ± 2ºC / 75%RH ± 5%RH (room temperature) in the absence of light.

Drug product stability encompasses chemical, physical, microbiological, therapeutic and toxicological stability not only of the drug substance, but when taking into account of the excipients, also the drug product (14). Stability studies should be performed for desired drug concentration and in real storage conditions (storage temperature, duration and type of container). The physical stability is assessed from changes in appearance, colour or odour, while the chemical stability is determined using an adequate analytical method for drug quantification (10). Microbiological stability should be conducted in extemporaneous oral formulations containing no or insufficient preservatives and be stored at room temperature over an extended period (10,15). This study focuses on the physical, chemical and microbiological stabilities and to confirm that the new formulation for the morphine oral suspension is suitable and stable.

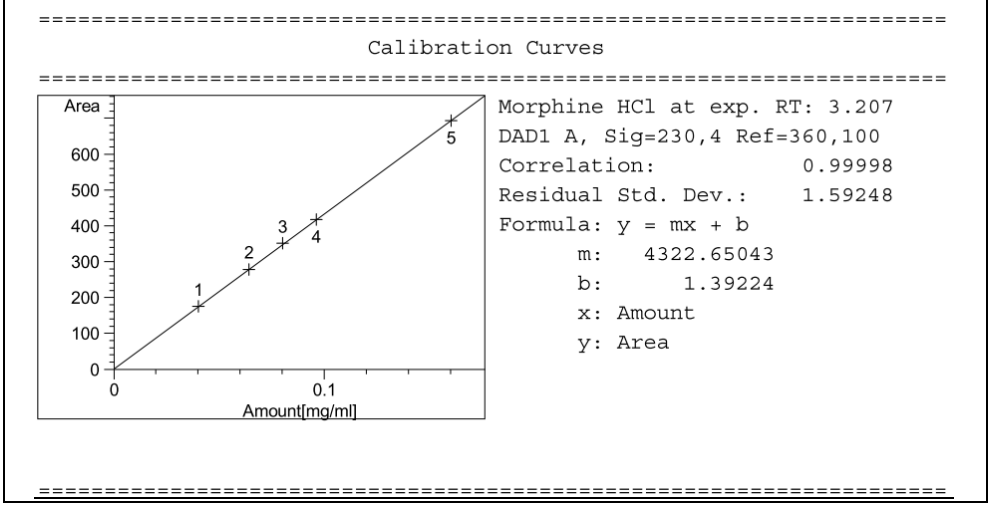
Analytical Method and Equipment

The content of morphine hydrochloride in the oral suspension was assayed by high-performance liquid chromatography (HPLC) method with reference to the British Pharmacopoeia and the content of morphine hydrochloride was set at 90 to 110% of the stated amount (16). The HPLC method for the analysis of morphine in this study was validated in a previous short-term stability study of extemporaneously prepared morphine oral suspension using the above formulation. The evaluation of the analytical method validation includes linearity, accuracy and system suitability (**Table 1**). A range performed on the HPLC system has confirmed the linearity of the method ($R^2 = 0.99998$) (**Figure 2**).

Table 1: Results of analytical method validation

Test Parameter	Validation Results	Acceptance Limits
Linearity & Range		
	R^2 = 0.99998 Intercept = 0.40% of the response of 100% (working) concentration	R^2: Not less than 0.999 Intercept: NMT 2% of the response of 100% (working) concentration
Accuracy		
Spiking of placebo 9 determination (3 replicates / 3 concentration)	99.3%, 99.6%, 99.7%, 98.1%, 99.0%, 98.7%, 100.4%, 101.1%, 100.8%	% recovery: 98 - 102% of label or mean from precision
System Suitability		
System Precision	RSD of detector response = 0.07%	RSD of detector response: NMT 2%
	RSD of retention time = 0.08%	RSD of retention time: NMT 1%
Peak Performance		Analyte
	k' = 2.215	k': NLT 1.5
	Resolution = 18.167	Resolution: NLT 2
	USP tailing = 1.344	USP tailing: NMT 2
	N = 5939	N: NLT 2000

Figure 2: Calibration curve of the HPLC assay method



The content of morphine hydrochloride was measured by HPLC-UV method after the sample of extemporaneous preparation was made throughout the stability study period. Samples were removed from each individual bottle on months 0, 1, 2, 3, 4, 5, 6, 9 and 12. A working reference standard of morphine hydrochloride was obtained from Johnson Matthey / Macfarlan Smith Limited, United Kingdom.

The HPLC system used for the analysis was an Agilent 1200 RRLC instrument with binary pump SL, autosampler SL, DAD SL detector, Thermostat Column Compartment SL and chemstation. The chromatographic separation used was Zorbax Eclipse XDB-C18 (4.6mm ID x 100mm, 3.5µm). The DAD detector operated at 230nm. The mobile phase consisted of a mixture of 65 volumes of 0.005M sodium heptanesulfonate buffer adjusted to pH 2.6 with orthophosphoric acid 85%

and 35 volumes of methanol. The mobile phase was delivered at a flow rate of 1ml/min. Samples were filtered before HPLC analysis and the injection volume as 5µL.

Physicochemical Stability

The physical and chemical tests (such as visual appearance, odour, pH and morphine content) were assessed at time 0, 1, 2, 3, 4, 5, 6, 9 and 12 months during storage at both temperatures. The morphine oral suspensions were examined at each sample time for any change in appearance (colour and clarity) or odour. The pH was periodically checked during storage at for both temperatures using a pH meter. The extemporaneous preparation is considered stable if physical characteristics have remained fairly unchanged and assay of morphine hydrochloride has remained equal or above 90% of the original concentration during the storage period.

Microbiological Stability

Microbiological stability of the morphine oral suspension stored at 4ºC and 30ºC was studied at the interval of months 0, 1, 2, 3, 4, 5, 6, 9 and 12. The microbial limit test was designed according to the British Pharmacopoeia for non-sterile products to determine whether the total bacteria, total fungi and *Escherichia coli (E. coli)* in the extemporaneous preparation complies with the established specification for microbiological quality of this type of product (17).

RESULTS AND DISCUSSION

Physicochemical Stability

Morphine degrades in aqueous solutions with the formation of mainly pseudomorphine, to a lesser extent morphine-N-oxide and probably apomorphine and discolouration has been observed when degradation products are found in morphine solution (6,18,19). The results of the colour, clarity and odour of the morphine oral suspension remained fairly unchanged and no precipitation was observed in any of the samples throughout the 12 months at both storage conditions (**Table 2**). The orange taste and sweetness of the morphine oral suspension were quite the same throughout the stability study period. Morphine salts are sensitive to change in pH and morphine is liable to be precipitated out of solution at alkaline pH (2). Vermeire and Remon (1999) also concluded that the degradation of morphine is accelerated at higher pH of the solution, whereas temperature and light have only a minor influence on the degradation rate (18). The results from this study confirmed that the pH values of the morphine oral suspension remained fairly constant (pH3.984 – 4.082) at both temperatures (**Table 3**).

Table 2: Visual appearance and odour of morphine oral suspension

Time (Months)	4ºC			30ºC		
	Colour	Clarity	Odour	Colour	Clarity	Odour
0	Off white	Opaque	Orange	Off white	Opaque	Orange
1	Off white	Opaque	Orange	Off white	Opaque	Orange
2	Off white	Opaque	Orange	Off white	Opaque	Orange
3	Off white	Opaque	Orange	Off white	Opaque	Orange
4	Off white	Opaque	Orange	Off white	Opaque	Orange
5	Off white	Opaque	Orange	Off white	Opaque	Orange
6	Off white	Opaque	Orange	Off white	Opaque	Orange
9	Off white	Opaque	Orange	Off white	Opaque	Orange
12	Off white	Opaque	Orange	Off white	Opaque	Orange

Table 3: pH of morphine oral suspension		
Time (Months)	4ºC	30ºC
0	4.075	4.075
1	4.080	4.074
2	4.073	4.082
3	4.074	4.060
4	4.070	4.036
5	4.068	4.040
6	4.082	4.041
9	4.036	3.984
12	4.050	4.001

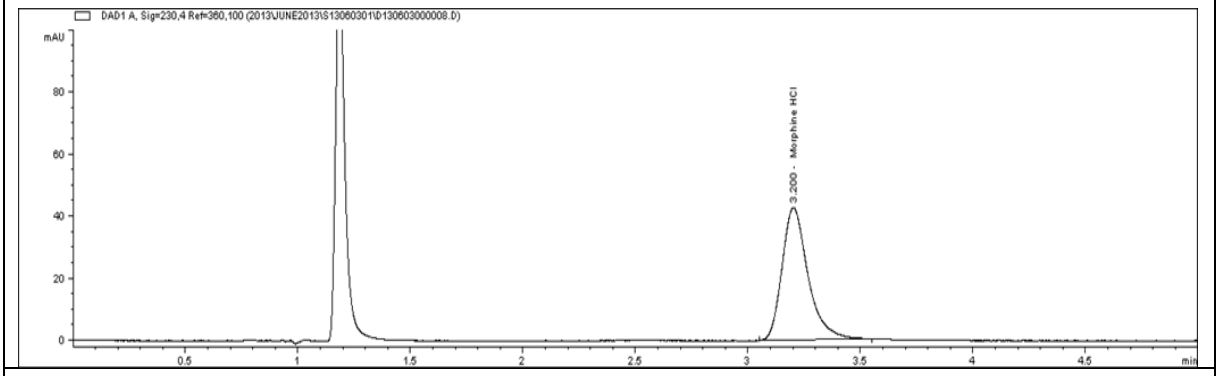
Table 4: Concentration of morphine oral suspension		
Time (Months)	4ºC	30ºC
0	102.8%	102.8%
1	97.0%	97.0%
2	99.3%	101.0%
3	95.1%	95.6%
4	96.1%	96.6%
5	101.4%	97.0%
6	99.5%	96.6%
9	96.1%	96.0%
12	95.5%	96.2%

The morphine hydrochloride content for all tested samples from the morphine oral suspension were all above 95% throughout the 12 months period for both temperatures (**Table 4**). Even though the rate of chemical degradation usually increases with temperature (11), there were no significant differences in the assay results between the two storage conditions to establish any possibility of degradation during storage.

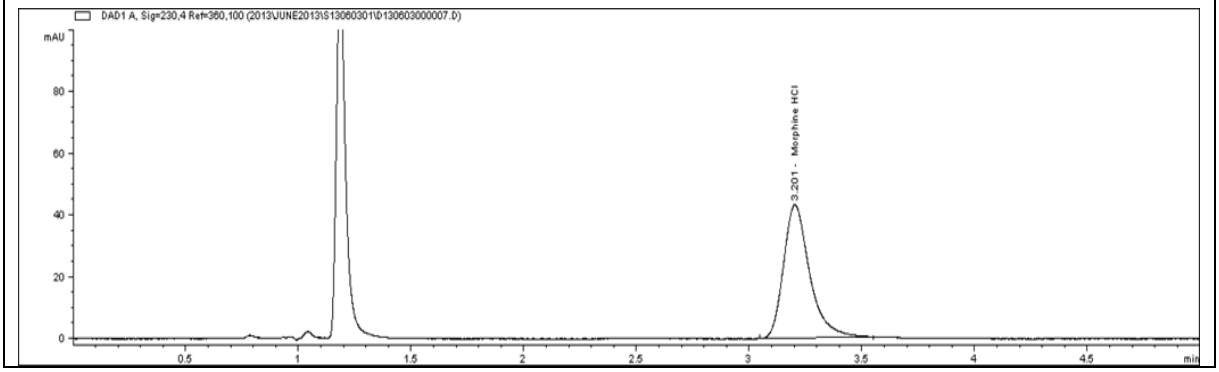
The analytical results of this stability study proved that the HPLC method developed for the analysis of morphine content in extemporaneous preparation to be adequate. The chromatograms illustrated below showed that the HPLC method to be selective for the purpose of this study with minimal interference from the excipients in the formulation (**Figure 3**). The chromatograms of tested samples at the different intervals throughout the stability study period revealed no other peak that could be attributed to a possible morphine degradation compound.

Figure 3: Chromatograms of morphine standard solution and extemporaneously prepared morphine oral suspension

Morphine standard solution



Morphine oral suspension



These results confirmed that the temperature has little effect on the physical and chemical stabilities of morphine in the oral suspension and the morphine content is relatively stable at acidic pH. Storage in the refrigerator may not be considered necessary. The extemporaneous preparation of morphine oral suspension remains stable when stored at room temperature in the same container closure system. Morphine solutions should preferably be stored at room temperature in order to avoid precipitation at low temperatures and water evaporation at higher temperatures causing increase in morphine concentration when store in polymer reservoirs (18).

Microbiological Stability

No microbial contamination was observed in all samples of morphine oral suspension during the 12 months study period for both temperatures (**Table 5** and **6**). The results showed that the microbial quality was within the test limits according to the British Pharmacopoeia (17). The total viable aerobic bacteria count was kept low and total yeast and mould count was minimal. *E. coli* was absent throughout the study period. These results shows that the preservatives of the extemporaneous preparation were effective against bacteria and fungi and the morphine oral suspension is microbiologically stable at both temperatures for up to 12 months.

Table 5: Microbial results of morphine oral suspension (4ºC)			
Time (Months)	Total aerobic bacteria (Not more than 200cfu/g)	Total yeast & mould (Not more than 20cfu/g)	*E. coli* (Absence in 1g)
0	<10cfu/g	<10cfu/g	Conforms
1	<10cfu/g	<10cfu/g	Conforms
2	<10cfu/g	<10cfu/g	Conforms
3	<10cfu/g	<10cfu/g	Conforms
4	<10cfu/g	<10cfu/g	Conforms
5	<10cfu/g	<10cfu/g	Conforms
6	<10cfu/g	<10cfu/g	Conforms
9	<10cfu/g	<10cfu/g	Conforms
12	<10cfu/g	<10cfu/g	Conforms

Table 6: Microbial results of morphine oral suspension (30ºC)			
Time (Months)	Total aerobic bacteria (Not more than 200cfu/g)	Total yeast & mould (Not more than 20cfu/g)	*E. coli* (Absence in 1g)
0	<10cfu/g	<10cfu/g	Conforms
1	<10cfu/g	<10cfu/g	Conforms
2	<10cfu/g	<10cfu/g	Conforms
3	<10cfu/g	<10cfu/g	Conforms
4	<10cfu/g	<10cfu/g	Conforms
5	<10cfu/g	<10cfu/g	Conforms
6	<10cfu/g	<10cfu/g	Conforms
9	<10cfu/g	<10cfu/g	Conforms
12	<10cfu/g	<10cfu/g	Conforms

Formulation Stability

The new formulation for extemporaneous preparation chosen for this study is simple and ideal for any pharmacist in UKMMC to prepare when compared to the old formulation consisting of morphine powder, glycerine, lemon oil, alcohol, water and syrup simplex. No published information is available to support the stability of the old formulation and to justify the shelf-life. Furthermore, traditional use of syrup BP (syrup simplex) as a suspending agent is not recommended as the typical pH of syrup BP is approximately 7.5 to 9.5 and does not promote morphine stability (19).

Preechagoon *et. al.* (2005) have studied the formulation development and stability testing of oral morphine solution using a preformulation approach (20). The study has highlighted that the pH of the solution is a major factor influencing morphine stability and masking of the bitter taste of morphine is another challenge (20). Even though the formulations have been demonstrated to be stable throughout the study period, some may consider the formulations from this study to be too complex for use at dispensary level (19).

The flavour and sweetener from the commercial vehicle, X-Temp Oral Suspension System were sufficient to mask the bitter taste of morphine in the extemporaneous preparation. Besides, the commercial vehicle is buffered to a slightly acidic pH (pH~4.4) and this pH helps to reduce the degradation process of morphine in solution.

CONCLUSIONS

The results from the physical, chemical and microbiological stability studies confirmed that the extemporaneous of morphine oral suspension using X-Temp Oral Suspension System is stable for up to 12 months when packed in HDPE bottles with polypropylene caps and stored at both 4ºC and 30ºC. The extemporaneous preparation can now be prepared with ease by compounding pharmacists in the hospitals using X-Temp Oral Suspension System with validated stability and proven shelf-life. This new evidence will be made available and the protocol can be standardized in the prescribing and compounding practices among the hospitals to provide a safe, effective and quality morphine oral suspension to the patients.

This study not only addressed the chemical, physical and microbial stability, it has also dealt into other parameters including palatability, excipient suitability (e.g. alcohol free for children, sugar free for diabetic patients) and interactions with packaging materials of an extemporaneous oral liquid. Visual appearance, smell, taste and mouth feel all have a big influence on patient acceptance and compliance, especially in the paediatric patients and are as important factor to consider in the development of a suitable extemporaneous preparation (13).

Although some of the risks associated with extemporaneous compounding has been addressed, there are still other inherent risks in compounding which include using incorrect formulation and calculations, selecting incorrect drugs and using incorrect quantities (8,21). Therefore, proper guidelines with focus on quality assurance and quality control practices should be put in place for every compounding pharmacy to deliver consistent, safe and quality products (22).

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