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Research Article

Formulation Development of Morphine Sulfate Sustained-Release Tablets and Its Bioequivalence Study in Healthy Thai Volunteers

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Abstract. The objectives of this study were to develop morphine sulfate sustained-release tablet formulations and to evaluate the bioequivalence compared with a commercial brand. The physicochemical properties of the formulated and commercial tablets were determined and compared. The bioequivalence investigation was carried out in 15 healthy male volunteers who received a single dose in a randomized two-way crossover design. After dosing, serial blood samples were collected for a period of 24 h. Morphine concentration was assayed by high-performance liquid chromatography with electrochemical detector. The log-transformed C_{max} and AUC_s were statistically compared by analysis of variance, and the 90% confidence intervals (CIs) of the ratio of the log-transformed C_{max} and AUC_s between the most promising developed formulation and the commercial product were determined. It was found that the dissolution rate profile of a developed formulation was similar to the commercial brand. Their similarity and difference factors were well within limits. In the bioequivalence study, the AUC_{last} and AUC_{inf} between the test and the reference products were not statistically different ($p=0.227$ and $p=0.468$, respectively), with the 90% CIs of 83.4–102.6% and 87.7–139.4%, respectively. However, the C_{max} of the two formulations was significantly different ($p=0.019$). The 90% CI of the developed formulation was 72.0–93.0% compared to the commercial product. *In vitro* dissolution of locally prepared morphine sulfate sustained-release tablets was comparable to commercial brand. However, the results justified the conclusion of lack of bioequivalence of the developed product to the commercial one.

KEY WORDS: bioequivalence; formulation development; morphine sulfate; sustained-release tablet.

INTRODUCTION

Pain can be an unrelenting torture, particularly whenever it appears concurrently with a terminal disease, such as cancer. Morphine remains the most important opioid analgesic presently available. It is recommended as the drug of choice for moderate and severe pain by the World Health Organization since 1986 (1). However, it has a short elimination half-life of only 1.5–2.5 h (2), leading to difficulties in clinical pain management. There was a study that supported that sustained-release morphine tablets administered every 12 h can replace an immediate-release morphine solution administered every 4 h (3). Yue *et al.* (4) demonstrated that oral treatment with sustained-release morphine hydrochloride in patients with cancer pain is effective, safe, and convenient and can improve the quality of life. At the present time, there are several oral sustained-release preparations of morphine with recommended dosing intervals of either 12 or 24 h. It is apparent that preparations of sustained-release tablets by incorporation of appropriate polymers are able to control the release rate of drug. In addition, the preparation of hydrophilic matrices, hydroxypropyl methylcellulose (HPMC) in particular, is the most popular technique employed in controlling drug release. This has been shown to be successful in the development of the controlled-release products including morphine (5,6).

Some studies demonstrated bioequivalence and non-bioequivalence between different brands of commercial morphine sustained-release products. For example, the comparative bioavailability of the two sustained-release products available in the USA, Oramorph SR® and MS

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Contin®, was evaluated using a multiple-dose, two-way crossover design in 26 healthy adult male volunteers. It was found that mean maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), and average serum concentrations of Oramorph SR® and MS Contin® met the 90% confidence intervals (CI, 80.00–125.00%) for the two, one-sided *t* test analysis (7). In another research, Oramorph SR® and MST Continus® were studied in 24 healthy male volunteers after a single oral dose (30 mg) given while fasting or after a high-fat breakfast (8). Overall relative bioavailability of the two formulations (log AUC) was within the acceptable 80.00–125.00% limits of bioequivalence in both fed and fasting conditions. The investigators reported no statistically significant differences between Oramorph SR® and MST Continus® in terms of bioequivalence or the incidence of adverse events. However, the log C_{max} between the two products was significantly different, and a non-bioequivalence was suggested. The bioequivalence of a single dose sustained-release morphine sulfate (30 mg), Skenan® capsules, and Moscontin® tablets was evaluated in another study in 12 healthy male volunteers in a randomized balanced two-way crossover design (9). From the AUC and C_{max} data, the results justified the non-bioequivalence of the two formulations.

Recent studies have demonstrated the bioavailability of the once daily product. Gourlay *et al.* (10) investigated the comparative bioavailability between Kapanol™ (24-h dose) and MS Contin® (12-h dose) in 24 patients with severe pain related to cancer. Even some of the pharmacokinetic parameters of Kapanol™ exhibited a significantly higher than those of MS Contin®; a once-a-day Kapanol™ provided the same degree of pain relief and morphine-related side effects as a 12-h MS Contin®. Therefore, it has been shown that some of the products are available in the market despite their bioavailability difference. Morphine sulfate extended-release (MSER; Avinza™), a once-a-day formulation, and MS Contin® (controlled-release morphine sulfate (CRM)), twice-a-day formulation, were comparatively evaluated in ten patients with chronic and moderate-to-severe pain (11). It was found that MSER and CRM demonstrated similar bioavailabilities (AUC) both in the form of morphine and its metabolites. However, a 19% lower C_{max}, a 66% higher minimum concentration (C_{min}), and a 44% lower peak-to-trough fluctuation (%FI) over the 24-h period were demonstrated in MSER compared to CRM. In addition, MSER maintained concentrations above 50% and 75% of the C_{max} longer than CRM. This suggested that commercial brands available in the markets still demonstrate the difference in bioavailability.

In Thailand, MST Continus® is the only commercial morphine sulfate tablet formulation available in the strength of 30 mg. As this product needs to be imported, therefore, the cost of cancer treatment is relatively high. Moreover, the shortage of the product even fabricates more problems for such treatment. The aims of the present study were thus to develop a morphine sulfate sustained-release tablet formulation and to evaluate its bioequivalence compared with the commercial brand, MST Continus®. The bioequivalence investigation was carried out in 15 healthy male volunteers who received a single dose of morphine sulfate sustained-release tablet in a randomized, two-way crossover design.

MATERIALS AND METHODS

Materials

Morphine sulfate was kindly supplied by the Narcotics Drug Control Division (Macfarlan Smith, Ltd., GlaxoWellcome, Boronia, Australia, batch number 27342). Materials used in this study were as follows: HPMC (E4M) and starch 1500 were bought from Rama production, Bangkok, Thailand; microcrystalline cellulose pH 101 and pH 102 were the products of AMC Corporation Ltd.®, Bangkok, Thailand; Eratab® was obtained from Erawan pharmaceutical Research and Laboratory Co., Bangkok, Thailand; lactose powder was from Praporn Darsuit Ltd., Bangkok, Thailand; hydromorphone HCl was purchased from Sigma-Aldrich, St. Louis, MO, USA; *di*-sodium phosphate and sodium phosphate were the products of BDH Laboratories Supplies, Poole, England; and methanol (high-performance liquid chromatography (HPLC) grade) was obtained from Merck, Bangkok, Thailand.

Methods

Development of Morphine Sulfate Sustained-Release Tablets

Direct compression was employed to prepare the developed tablets. Morphine sulfate was weighed and mixed with HPMC E4M and diluents, *i.e.*, microcrystalline cellulose pH 101 and pH 102, Eratab®, lactose powder, starch 1500, and spray-dried lactose in a plastic bag using geometric dilution technique for 15 min. The quantity of the polymer and those diluents per tablet are shown in Table I. Magnesium stearate was added and mixed for another 5 min. Tablets were compressed to a target weight of 200 or 250 mg using a single punch tableting machine (Yeo Heng, Co. Ltd., Thailand) with a 1/4-in. diameter punch. The hardness of the tablet was controlled at 7±1 kg. The prepared tablets were tested for weight variation (n=20), hardness (n=5), drug content (n=10), and thickness (n=10). Drug content of morphine sulfate sustained-release tablets was analyzed by measuring the absorbance of standard and samples at λ=275 nm using UV-visible spectrophotometer (Jasco model V-530, Tokyo, Japan).

Dissolution Tests and In Vitro Drug Release Characteristics

Drug release of the products was determined using USP type I dissolution test apparatus (Vankel 8000) at 100 rpm using 900 mL of 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8 as dissolution media which were maintained at 37± 0.5°C. The tablets were placed in the acid medium for 2 h. Five milliliters of the sample was drawn at regular time intervals and replaced with the same volume of prewarmed (37°C) fresh dissolution medium. After 2 h, fresh phosphate buffer pH 6.8 was added to replace the acid medium. Sampling was performed as previously described for up to 12 h. Morphine concentration was spectrophotometrically determined at 245 nm. The mean concentration of morphine from triplicates was calculated from the standard curves. The difference factor (f_1) and similarity factor (f_2) for the release of morphine were determined between the developed formulations and the reference product. The mechanisms of drug release from the matrix tablets were analyzed utilizing

Table I. Developed Formulations of 30 mg Morphine Sulfate Sustained-Release Tablets

Ingredient	Weight (mg); F1–F6					
	F1	F2	F3	F4	F5	F6
Morphine sulfate	30	30	30	30	30	30
HPMC E4M	62.5	75.0	62.5	50.0	50.0	54.0
Avicel® pH 101	–	–	–	66.0	70.0	66.0
Avicel® pH 102	95.8	105.0	105.8	–	–	–
Eratab®	–	–	–	25.0	28.0	28.0
Starch 1500	34.2	–	41.7	–	–	–
Lactose powder	–	–	–	27.0	20.0	20.0
Spray-dried lactose	25.0	37.5	7.5	–	–	–
Magnesium stearate	2.5	2.5	2.5	2.0	2.0	2.0
Tablet weight	250	250	250	200	200	200

the zero-order (Eq. 1), the Higuchi (Eq. 2), and the Korsmeyer–Peppas (Eq. 3) models as follows (12–14):

$$M_t = M_0 K_0 t \tag{1}$$

$$M_t = M_0 K_H t^{0.5} \tag{2}$$

$$M_t = M_0 K_K t^n \tag{3}$$

where M_t is the amount of the drug dissolved at time t, M_0 is the initial amount of drug in the solution, K_0 is the zero-order release constant, K_H is the Higuchi rate constant, K_K is the release constant, and n is the release exponent.

Determination of Plasma Morphine Concentration

An HPLC method utilizing reversed-phase chromatography coupled with coulometric detection (ESA, Coulochem II, Bedford, MA, USA) was developed for the determination of morphine in plasma (15). Hydromorphone was selected as an internal standard (16). The compounds were extracted using solid-phase extraction with C_{18} cartridges and separated on a reversed-phase C_{18} column (Zorbax®, 5 μm particle size, Agilent, Palo Alto, CA, USA) with mobile phase consisting of 69% buffer (5 mM sodium phosphate monobasic and 0.7 mM sodium dodecyl sulfate, pH 2.2) and 31% acetonitrile. The working electrode was set at 450 mV for analytical purposes. The limit of detection for morphine was 0.33 ng/mL. The linearity of a standard curve ranging from 2.0 to 50.0 ng/mL was relatively high (r^2=0.998). The assay showed good reproducibility and accuracy. The percent recovery of morphine (1.88–47.0 ng/mL) in plasma samples was 85.07–93.41%. For the intra- and inter-assay precision, variation was less than 12% for the lowest concentration (1.88 ng/mL).

Bioequivalence Study

Inclusion and Exclusion Criteria of Healthy Volunteers

Fifteen healthy male volunteers aged between 20 and 45 years were recruited. All were determined healthy according to physical examination and routine laboratory evaluation. The laboratory evaluation included complete blood count, hematocrit, blood urea nitrogen, serum creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, and hepatitis viral profile. Exclusion criteria included a history of alcohol or drug abuse. They must receive no prescribed medications within 2 weeks or nonprescription medications within 1 week before entry to the study and throughout the study period. All provided written informed consents prior to study participation.

Research Experiment

The protocol for the human studies has been reviewed and approved (number HE490135) from Khon Kaen University Ethics Committee for Human Research (Institutional Review Board Number, IRB00001189) and the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand. The study criteria were carried out following the Thailand Guideline for the Conduct of Bioavailability and Bioequivalence studies (17) in accordance with the principles of the Declaration of Helsinki and its amendments and the International Conference on Harmonization Guideline for Good Clinical Practice. A 2×2 crossover, open label, randomized design was performed in this study.

The volunteers arrived at an extra clinical unit at Srinagarind Medical School Hospital, Khon Kaen University, Thailand at 7 am and were randomized in a 1:1 ratio using a table of random numbers to receive a developed product followed by MST Continus®, or *vice versa*, with a 2-week washout period. Volunteers were fasted for at least 8 h before the study day. Blood samples were drawn by the following manner: a 20-G catheter (Jelco®, Medex Medical Ltd., Ascot, UK) was placed in a forearm vein, and a 10-mL blood sample was drawn into a heparinized plastic tube. The volunteers received a single 30-mg tablet of the study medication, given with 240 mL water at 8 a.m. Blood samples were drawn at 0 (pre-dose sample for baseline measurement), 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24.0 h. Water could be consumed any time after 2.5 h of drug administration. A standardized lunch and evening meal were served at 4 and 10 h after drug

Table II. Physical Properties of MST Continus® and Three Developed Formulations (mean ± SD)

Formulation	Thickness (mm); n=10	Weight (mg); n=20	Hardness (kg); n=5	Drug content (mg); n=10
MST Continus®	4.44±0.03	157.0±0.1	3.70±0.16	31.04±0.03
F4	3.51±0.02	202.9±1.3	6.87±0.21	30.13±0.60
F5	3.44±0.03	201.5±2.9	7.27±0.34	29.45±0.71
F6 (Morph)	3.45±0.02	202.4±2.3	6.87±0.41	29.83±1.16

administration. Plasma was obtained by centrifugation and stored frozen at −20°C until analysis.

Tolerability Assessments

Drug tolerability was assessed by a physician based on changes in findings on physical examinations, including vital sign measurements (blood pressure, heart rate, and pupil size). Any undesirable sign, symptom, or medical condition occurring after the start of the study was recorded regardless of suspected relationship to the study drug.

Pharmacokinetic Parameters and Statistical Analysis

Maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) were obtained from the observed data. Noncompartmental analysis was performed on morphine concentration using WinNonlin Professional version 5.1 (Pharsight Corporation, Mountain View, CA, USA) to determine the area under the plasma concentration–time curve from time 0 to the last quantifiable concentration (AUC_{last}) and AUC from time 0 to infinity (AUC_{inf}). Statistically significant differences of log-transformed C_{max}, AUC_{last}, and AUC_{inf} of the developed formulation and the original product were determined using analysis of variance (ANOVA) with a significant difference set at $p<0.05$. Ninety percent CIs were calculated for the ratios of the log-transformed C_{max}, AUC_{last}, and AUC_{inf} values of the two products to compare the statistical difference using two one-side t test. Bioequivalence was concluded if the 90% CIs for C_{max}, AUC_{last}, and AUC_{inf} were within 80.00% to 125.00%. In addition, relative bioavailability (F_{rel}), half-life ($t_{1/2}$), and mean residence time (MRT) were also determined.

RESULTS

Development of Morphine Sustained-Release Tablets

Tablet properties between the commercial brand and the most promising products (F4–F6) are illustrated in Table II. It was found that variations of weight, hardness, and drug content of the commercial brand were lower than those of the developed product. The content of morphine was uniform between the formulations at approximately 30 mg, with low standard deviations. The dissolution profile of F6 was most close to that of the commercial brand. For F6 and the original brand, the dissolution rates were practically the same for the first 4 h. Approximately 60% and 85% of morphine were dissolved in acid condition after 2 and 5 h in basic condition, respectively (Fig. 1).

Difference and Similarity Factors

The principal purpose of dissolution testing between the developed product and the original product was to achieve the similar profiles for the two products. Difference factor (f_1) can be calculated from percent difference of means of each point of sampling between the two products using Eq. 4, while similarity factor (f_2) can be calculated from Eq. 5 (18):

$$f_1 = \left[\left\{\sum_{t=1}^{n}|R_t - T_t|\right\} \Big/ \left\{\sum_{t=1}^{n} R_t\right\}\right] \times 100 \qquad (4)$$

$$f_2 = 50 \times \log\left[\left\{1 + (1/n)\left[\left\{\sum_{t=1}^{n}(R_t - T_t)^2\right\}^{-0.5} \times 100\right]\right.\right. \qquad (5)$$

where n is number of time points, and R_t and T_t are dissolution of reference and test products at time t. The acceptability of equivalence between the two products is that f_1 is close to zero and f_2 is between 50 and 100. If f_2 is greater than 50, it is considered that the two products share similar drug release behaviors. For the study between F6 and the commercial brand, the f_1 factor was relatively close to zero (f_1=2.76), and f_2 factor was 80.0. This implied no such difference of the dissolution profiles between the two products. Therefore, F6 was chosen for bioequivalence study as it gave similar dissolution profile compared to the original product (Fig. 1). The dissolution results are the major consideration for the selection of the developed formulations for bioequivalence study.

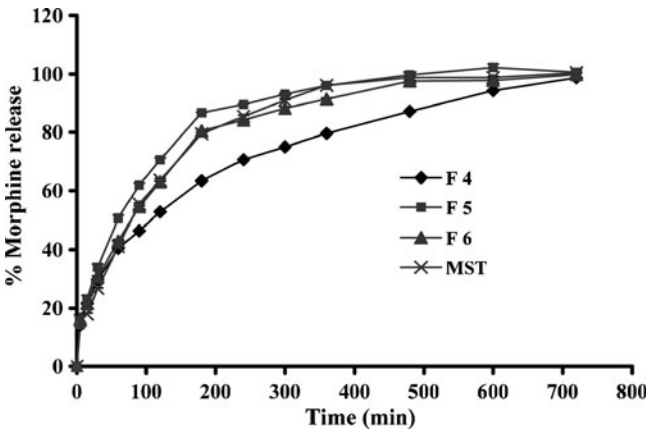

Fig. 1. Percentage of morphine release

Table III. Dissolution Release Kinetic Parameters of Morphine Between MST Continus® and the Three Selected Developed Formulations (0–12 h Period; Calculated from $n=13$)

	Korsmeyer–Peppas equation		Higuchi equation		Zero-order equation	
Drug	n	r^2	K_h	r^2	K_0	r^2
MST	0.689	0.923	4.05	0.918	0.130	0.725
F4	0.635	0.970	3.63	0.978	0.121	0.852
F5	0.676	0.975	3.96	0.890	0.124	0.673
F6 (Morph)	0.644	0.940	3.98	0.923	0.125	0.729

Identification of the Release Mechanism

The drug release kinetics of the developed formulations and the commercial brand are shown in Table III. The Higuchi model is applicable in the case where the release of drug is largely governed by diffusion through water-filled pores in the matrix. Regarding the Higuchi and zero-order release model, the MST Continus® and F6 were very close in rate constant, but the linearity value was not close to 1.0.

Bioequivalence Study

The mean age (±SD) of the volunteers was 24.8±8.8 years, and the body mass index was 21.8±2.8 kg/m^2. Figure 2 shows the mean (±SD) plasma morphine concentrations from 15 healthy volunteers after receiving a single dose of 30 mg morphine sulfate sustained-release tablets from both products. It was clear that the mean plasma morphine concentration of MST Continus® was higher than that of the developed product (Morph) from 1 to 8 h after drug administration. However, from 8 to 24 h period, the drug concentration profiles were very close. Interestingly, variation of the drug concentrations during the 24-h period of Morph was less than that of the commercial brand (standard deviation ranged from 0.91 to 3.15 ng/mL and from 0.66 to 4.03 ng/mL, respectively). Table IV illustrates individual subject AUC values for each treatment.

The mean ± SD of C_{max} of MST Continus® was significantly higher than that of Morph ($p=0.019$, Tables V and VI). This resulted in shorter T_{max} of MST Continus® compared to Morp. However, the mean AUC_{last} and AUC_{inf} of the two products was close (110.6±24.3 and 103.3±27.5 ng/mL.h; 141.6±48.9 and 146.4±56.1 ng/mL.h, respectively), and no significant difference was found ($p=0.227$ and $p=0.468$, respectively). The relative bioavailability of Morph compared to MST Continus® was 0.93 according to AUC_{last} mean values. The mean half-life of MST Continus® was shorter than that of Morp, which might result in longer MRT of Morph as shown in Table V. It can finally be concluded that C_{max} and MRT were statistically different between the two products.

The 90% CI ratio of C_{max} of the developed product and the commercial product was 72.0–93.0%, while the ratios of AUC_{last} and of AUC_{inf} were 83.4–102.6% and 87.8–139.5%, respectively (Table VI). It, thus, could be concluded that the two formulations were not bioequivalent since only AUC_{last} was complied with the bioequivalence criteria. Because of the low power of the test in AUC_{inf}, this might lead to the failure of the 80.0–125.0% range even though the AUC_{inf} of the two products were not statistically different ($p=0.468$, Table V).

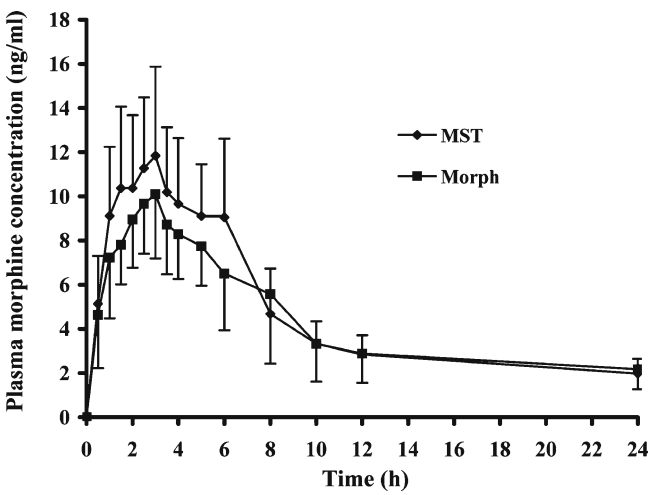

Fig. 2. Mean plasma morphine concentrations

DISCUSSION

Development of Morphine Sustained-Release Tablets

It was observed that not only type and percentage of polymer affected the dissolution behavior of morphine but also the diluents used in the formulation. The type and amount of polymer and direct compressible diluents were selected regarding their properties on tablet preparation and

Table IV. Individual Subject AUC Values for Each Treatment After Received Developed and Original Products

Subject No.	AUC_{0-24} (ng/mL.h; MST Continus®)	AUC_{0-24} (ng/mL.h; Morph)
1	120.3	100.4
2	127.4	115.3
3	122.1	178.9
4	156.0	108.7
5	148.2	142.2
6	96.7	72.7
7	126.1	123.9
8	91.5	132.9
9	105.8	124.4
10	93.6	127.2
11	175.4	142.0
12	157.1	170.1
13	89.2	95.4
14	105.8	137.1
15	102.1	85.0

Table V. Pharmacokinetic Parameters Between MST Continus® and Morph from 15 Healthy Male Volunteers

Parameter	MST Continus®	Morph	*p* value
C_{max} (ng/mL)	14.2±3.5	11.6±2.3	0.019*
C_{max} (range, ng/mL)	8.2–20.2	9.2–15.4	–
T_{max} (h)	2.8±1.5	3.5±2.0	0.312
AUC_{last} (ng/mL.h)	110.6±24.3	103.3±27.5	0.227
AUC_{last} (range, ng/mL.h)	85.9–158.9	76.7–151.9	–
AUC_{inf} (ng/mL.h)	141.6±48.9	146.4±56.2	0.468
%Relative bioavailability	(AUC_{last}) Morph/MST Continus®=0.93		–
*t*1/2 (h)	10.7±5.7	13.1±6.8	0.233
MRT (h)	7.8±1.1	8.9±0.9	0.022*

*Significant difference at $p \leq 0.05$

sustained-release control. After several attempts on type and amount of the ingredients, it was found that apart from HPMC E4M as controlling polymer, Avicel pH 101, Eratab®, and lactose (F6) were the appropriate direct compressible diluents to control the release rate of the developed morphine formulation. Inert ingredients not only affected the dissolution rate but also the shape of the tablet after contacting the dissolution medium. It was found that the shape of tablets from formulations with starch 1500, spray-dried lactose, and microcrystalline cellulose (F1, F2, and F3) changed into two layers in 30 min after the tablets were immersed in acid medium, whereas this phenomenon was not observed in formulations containing Eratab®, lactose, and microcrystalline cellulose (F4, F5, and F6). Tablets containing microcrystalline cellulose pH 101 showed no problem of flowability during tableting. The tablets of F6 swelled in acid medium, and the shape was round in both acid and basic media. However, it was observed that the size and shape of MST Continus® tablets changed minimally in both media during the 12-h study.

Identification of the Release Mechanism

The magnitude of the release exponent "*n*" in the formula indicates the release mechanism according to the mathematical models (Fickian diffusion, case II transport, or anomalous transport). The limits considered were $n=0.45$ indicating a classical Fickian diffusion-controlled drug release and $n=0.89$ indicating a case II relaxational release transport or non-Fickian (zero-order release). Values of *n* between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport (19). If the model fit to the Korsmeyer–Peppas equation, the combined effect of diffusion and erosion mechanisms for drug release is obtained. From the release exponent in the Korsmeyer–Peppas model, the *n* value of MST Continus® and F6 are 0.689 and 0.644, respectively.

It can be suggested that the mechanism that led to the release of morphine was an anomalous transport with constant release rate adequate for a sustained-release dosage form. The correlation (r^2) was used as an indicator of the best fit for each of the models considered (Table III). The release of morphine (Fig. 1) apparently follows Korsmeyer–Peppas model ($r^2>0.92$), but not zero-order kinetics for all formulations. However, looking at the negligible variation of r^2 values for the release of morphine, the release data analysis applying these mathematical models can be purely empirical, and no definitive conclusion can be drawn concerning the dominating mass transport mechanism.

Table VI. The Statistical Differences and 90% CI of the Pharmacokinetic Parameters Between MST Continus® and Morph from 15 Healthy Male Volunteers

Parameter	ANOVA (*p* value)	90% CI	Power (%)
C_{max}	0.019	72.38–93.93	88.57
AUC_{last}	0.227	83.44–102.63	96.94
AUC_{inf}	0.468	87.77–139.47	47.69

Bioequivalence Study

It can be considered that although the *in vitro* dissolution profiles among Morph and the commercial brand were similar, the *in vivo* kinetics may be different. This may be because the content of the original tablets was approximately 4% higher than the developed product. The absorption of morphine can also play a vital role in differences of kinetic parameters between the two products. The commercial brand may contain some absorption enhancers in the formulation. In addition, it may be because the dissolution test media are not exactly the same as *in vivo* condition.

Although some studies have demonstrated bioequivalence of commercial morphine sulfate products with similar or non-similar dosage forms (7,10), it was found that at least a couple of studies reported lack of bioequivalence among the marketed products (8,9). One reason might be from the difference in the mean C_{max} between the products as that reported by Drake *et al.* (8): the mean C_{max} of Oramorph SR tablet (13.9 ng/mL) was approximately 30% higher than that of MST Continus® tablet (10.7 ng/mL). Moreover, the considerable variability between studies in terms of different formulations, different types of volunteers (healthy volunteers and patients), and different measurement methods might result in varied plasma morphine concentrations after oral administration in various reports.

Even though our developed formulation (Morph) was not bioequivalent to the commercial product, its maximum plasma morphine concentration seemed to be promising. Plasma morphine concentrations of F6 of over 6 ng/mL could be observed between 1 and 8 h which was comparable to, or

longer than, 1 to 5 h reported by Drake *et al.* (8) both from MST Continus® and Oramorph®. As it has been reported, the maximum concentration, corrected by dose for controlled-release dose of morphine, was 3.2 nmol/L/mg, with a wide range between 1 and 10 nmol/L/mg (20). Our formulation offered a maximum plasma morphine concentration, corrected by dose, of approximately 1.5 nmol/L/mg. Although those results are from different studies, we are certain that morphine concentration from our developed product would be able to present analgesic properties in patients. However, interchangeable product may not be suggested from this study. Further study in patients must be therefore performed to prove the efficacy of the developed product compared to the original product. In addition, the study demonstrates that the method of tablet preparation in this study can be applied for all developing and under-developed countries to produce morphine sustained-release tablet for their local people. It would be sure that the cost of cancer treatment, in particular, would reduce, and this could strongly support the patient needs.

Adverse Events

Adverse events were reported by four of the 15 volunteers receiving both Morph and MST Continus®. The most common adverse effects were nausea and headache. Those volunteers were asked to lie on beds while no medication was required. The symptoms were relieved soon after. Most adverse effects were observed at time of peak drug concentration. Low pulse rate was observed in one volunteer who received Morph; however, no sign of serious consequence was detected.

CONCLUSION

This finding confirmed that HPMC E4M and direct compression method are good choices to prepare and control the release of morphine from sustained-release tablets. The similarity of the release profile between the commercial brand and the promising developed product was revealed as determined from the difference and similarity factors. However, only the AUC_{last} was found to be equivalent between the two products but not the C_{max} of morphine concentration. Nonetheless, the pain control efficiency of the promising developed formulation should be further clinically evaluated with cancer patients. This research will be evoked hopefully to the developing countries where they need to develop their own pain killer preparation for poor patients.

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