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Full Length Research Paper

Quantification of propranolol in rat plasma by LC-MS/MS using tramadol as an internal standard: Application to pharmacokinetic studies in TAA-induced liver fibrotic rats

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A simple, rapid and selective liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) is developed and validated for quantification of propranolol without the sample extraction step in rat plasma using tramadol as an internal standard (IS). The analytes are separated using an isocratic mobile phase which consist of methanol and 10 mm ammonium formate (70/30, v/v) on an isocratic UK-C18 (Imtakt Unison 2.0 × 50 mm, 3 µm) column and was analyzed by MS/MS in the multiple reaction monitoring (MRM) mode using the transitions of respective $(M+H)^+$ ions, m/z 260.0→116.2 and m/z 264.2→58.2 for quantification of propranolol and IS, respectively. The standard calibration curves showed good linearity within the range of 2.0 to 800.0 ng/ml (r^2 = 0.999, $1/x^2$ weight). The lower limit of quantification (LLOQ) was 2 ng/ml. The retention time of propranolol and IS were 1.12 and 0.939 min which means that it is the potential for the high-through put potential of the proposed method. In addition, no significant metabolic compounds were found to interfere with the analysis. Acceptable precision and accuracy were obtained for the concentrations over the standard curve range. The validated method was successfully applied for the pharmacokinetic studies after 2 mg/kg of propranolol HCl in the thioacetamide (TAA)-induced fibrotic rats.

Key words: Propranolol, liquid chromatography, mass spectrometry, pharmacokinetics, thioacetamide, liver fibrosis.

INTRODUCTION

Propranolol ([RS]-1-(1-methylethylamino)-3-(1-naphthyloxy) propan-2-ol]) is a competitive non-selective β-adrenergic blockers used to treat hypertension, angina, cardiac arrhythmia, anxiety and thyrotoxicosis. It was the

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first successful β-blocker developed (Black et al., 1964) and is also one of the most widely prescribed β-blockers approved in the US (Koshakji and Wood, 1986; Shin and Johnson, 2007). Despite complete absorption, propranolol has a variable bioavailability due to extensive first-pass metabolism and is eliminated almost exclusively by hepatic metabolism by three routes called a naphthalene ring hydroxylation, N-dealkylation of the isopropylamine side chain oxidation and O-glucuronidation (Thompson et al., 1981; Walle et al., 1985; Masubuchi et al., 1993). Therefore, hepatic impairment will increase its bioavailability and high blood concentration that has more than 18 metabolites, with at least four of these having pharmacological activities (Silber et al., 1983). Among these metabolites, the main metabolite, 4-OH propranolol, has a longer half-life up to (5.2 to 7.5 h) than the parent compound (3 to 4 h) which is also pharmacologically active. The duration action of propranolol after single oral dose is longer than the half-life and may last up to 12 h, if the dose is high enough and effective serum/plasma levels encountered between 10 to 100 ng/ml with toxic levels above 2 µg/ml in clinical situations. Many high-performance liquid chromatography (HPLC) methods for the analysis of propranolol in human plasma using both fluorescence (Rosseel and Bogaert, 1981; Rekhi et al., 1995; Kim et al., 2001) and UV (Wolf-Coporda et al., 1987; Walshe et al., 1996) detection have been described. HPLC-fluorescence detector may provide the selectivity and sensitivity necessary for routine analysis of propranolol in the blood (Hedeen et al., 1991).

Propranolol concentrations in the plasma encountered during routine propranolol therapy may range from a low 1.0 ng/ml to above 100 ng/ml, and several methods have been reported for the determination of propranolol in plasma (Rekhiet al., 1995). Probably, HPLC-UV (Zhou et al., 2002; El-Saharty, 2003; Delamoye et al., 2004) or fluorescence (Ranta et al., 2002; Satinsky et al., 2007) detection would be a more suitable choice for the routine β-blockers analysis. Due to the complex matrix of biological samples, a pretreatment procedure such as liquid-liquid extraction (Braza et al., 2000; Zhouet al., 2002; El-Saharty, 2003) pre-column clean-up (Mislanova and Hutta, 2003) and solid-phase extraction (SPE) (Satinskyet al., 2007; Hefnawy et al., 2011; Vukovic et a.l, 2012) were required for β-blockers separation and concentration before HPLC analysis.

Recently, combined techniques such as liquid chromatography (LC) and mass spectrometry (MS) have considerably improved analytical selectivity and sensitivity. LC-MS/MS facilitates rapid data turn around and requires minimal method development. Unfortunately, due to the complexity and protein components of biological fluids, the direct injection of these samples is not compatible with most chromatographic systems (Mullett, 2007). Biological samples are problematic due to the irreversible absorption of proteins on the stationary phase, resulting in the substantial loss of column efficiency and increase in back pressure (Souverain et al., 2004). Therefore, appropriate sample preparation is critical and is a key consideration for the development of quantitative HPLC methods for measuring drugs in biological fluids. The role of sample preparation also continues to be an important area for development, since the increase of acceptance of high-throughput instrumentation, such as LC-MS/MS, has shifted the analysis bottleneck backward towards sample preparation (Berna et al., 2002). One of the more common procedures for overcoming the difficulties associated with high complex and proteineous biological fluids is simple precipitation of proteins with an organic solvent, with or without an acid, followed by centrifugation (Gage and Stopher, 1998; Jayewardene et al., 2001).

This research paper describes a simple, rapid and sensitive LC-MS/MS for the analysis of propranolol in rat plasma obtained from male thioacetamide (TAA)-induced liver fibrotic rats after dosed intravenously with propranolol, with simple precipitation mobile phase, followed by centrifugation and it s application to pharmacokinetic studies.

MATERIALS AND METHODS

Chemicals

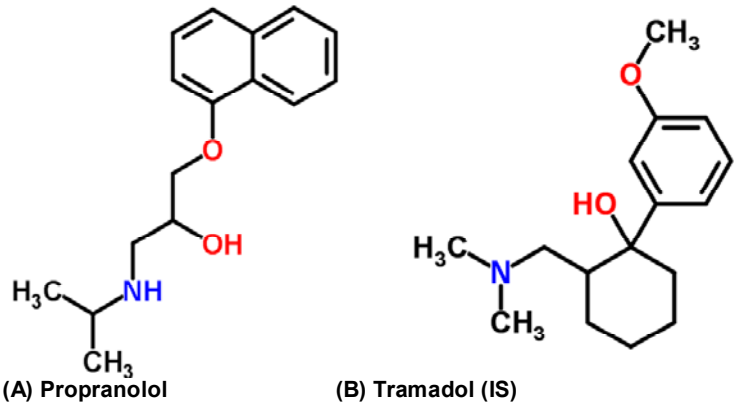
Propranolol HCl ($C_{16}H_{21}NO_2$•HCl, MW=260.0 g/mol) and tramadol HCl (IS, internal standard, $C_{16}H_{25}NO_2$•HCl, MW=263.2 g/mol) were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA), respectively (Figure 1). Purity was found to be more than 99% of all the compounds. Acetonitrile, ammonium formate and methanol are all HPLC-grade purchased from Sigma Co. (St. Louis, MO, USA) while other reagents and solvents used were of analytical grade. All aqueous solutions including the buffer for the HPLC mobile phase was prepared with water purified by Milli-Q water purification system (Millipore, Milford, MA, USA).

Stock solutions and quality control standards

Primary stock solutions of propranolol hydrochloride and IS were prepared with methanol solution to a final concentration of 1 mg/ml and 10 µg/ml, respectively and stored at -20°C. A set of six non-zero calibration standards ranging from 2.0 to 800 ng/ml were prepared in blank rat plasma, with an appropriate amount of propranolol. The quality control (QC) samples were prepared in blank rat plasma at its concentrations of 10, 100 and 400 ng/ml. Blank rat plasma was tested before spiking to ensure that no endogenous interference was found proximal to retention times of propranolol and IS.

Sample preparation

After dilution of stock solution of propranolol to a concentration of 2.0 to 800 ng/ml with blank plasma, 50 µl aliquot of rat plasma was pipetted into a screw cap glass tube. Briefly, 100 µl of acetonitrile (containing IS with concentration of 100 ng/ml) were added to the 80 µl aliquot of rat plasma for deproteinization. The mixture was briefly vortex-mixed for 10 s, followed by centrifugation at 13,000 rpm for 10 min. The supernatant was transferred to another set of



(A) Propranolol **(B) Tramadol (IS)**

Figure 1. Chemical structures of (A) propranolol [MW = 259.34 g/mol, $C_{16}H_{21}NO_2$, 1-(isoprophylamino)-3-(1-naphthyloxy)-2-propanol and (B) tramadol [IS, MW = 263.4 g/mol, $C_{16}H_{25}NO_2$, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol.(from ChemSpider free chemical data base)

clean glass tubes and then 200 µl of mobile phase added and vortex-mixed. After centrifugation at 13,000 rpm for 10 min, 2 µl of the supernatant were directly injected into the LC-MS/MS.

LC-MS/MS analyses

The LC system used was an Agilent (Agilent Technologies, Inc., Palo Alto, CA, USA) chromatograph equipped with an isocratic pump (1200 series) and interfaced with an autosampler (Reliance, Spark, Holland). The analytical column was an isocratic UK-C18 (Imtakt Unison 2.0 × 50 mm, 3 µm) column (SIS Inc., Co. Ringoes, NJ, USA) which was placed in an oven at 40°C. The mobile phase consisted of methanol [10 mm ammonium formatted with 0.1% formic acid (70:30, v/v)] and the flow rate was 250 µl/min. MS analysis was performed using an AB Sciex 400 QTRAP™ mass spectrometer system (Applied Biosystems, Foster City, CA, USA) equipped with an electrospray ionization (ESI) interface and Ionics EP 10+ system, and operated in the positive ionization mode. The ion source parameters were set as follows: curtain gas = 40 psi, GS1 = 50 psi and GS2 = 50 psi, ion spray voltage = 5500 V, ion source temperature = 350°C, collision-activated dissociation (CAD) = medium. This system was set up in multiple-reaction monitoring (MRM) mode, monitoring the transitions *m*/*z* 260.13 → *m*/*z* 116.1 and *m*/*z* 264.20 → *m*/*z* 58 for quantification of propranolol and IS, respectively. Data acquisition and analysis were performed using the analyst software peak simple chromatography data system version 1.4.1 (Applied Biosystems, Foster City, CA, USA). Total chromatographic run time per sample was about 3 min.

Assay validation

Assay validation was performed according to the Food and Drug Administration (FDA) guidance on bioanalytical methods validation (FDA, 2001). Linearity was determined using a linear least-square regression with $1/x^2$ weighting, which was performed on the peak area ratios of propranolol/IS versus propranolol concentrations of the six rat plasma standards. The sensitivity of the method was expressed as the lowest limit of quantification (LLOQ) that could be quantitatively determined with acceptable accuracy and precision. The accuracy and precision were assessed by analyzing four concentrations of QC samples with 2.0 to 800 ng/ml from five different validation batches and was calculated using one-way analysis of variance (ANOVA). Specificity was performed and six randomly selected blank rat samples collected under controlled conditions were passed through the similar extraction procedures. The samples were analyzed to determine the extent to which endogenous plasma components could interfere with the analytes or IS at the retention time. To evaluate the inter-day precision and accuracy, validation control samples with drug concentration of 2.0, 10, 100 and 400 ng/ml propranolol and IS (100 ng/ml) solutions were analyzed together with one independent calibration curve. The accuracy and precision of the inter-day assay were evaluated at the same concentration and was calculated for five different days. Inter- and intra-day precision were expressed as relative standard deviation (RSD). The accuracy was expressed as the percentage ratio between the experimental and nominal concentrations for each sample. The lowest limit of quantification (LLOQ) was defined as the lowest plasma concentration of each propranolol analyzed with an error of 20% or lower, that corresponds to a signal five times greater than the analytical background noise in our experiment (FDA, 2001).

Pharmacokinetic study

Animals were handled and housed in a protected environment in conventional plastic cage with free access to food and water. The animals were maintained at a temperature of 22 to 25°C with a light cycle of 12 h of light and 12 h of darkness (12L:12D), with the lights on at 0700 h and off at 1900 h (Wersinger and Martin, 2009). Hepatic fibrosis was induced by intraperitoneal injection of thioacetamide (TAA, 200 mg/kg), 2 times per week, during 12 weeks and then 3 times per week during 7 and 11 weeks in minimal and severe liver fibrotic groups, respectively. The fibrotic change of each animal were confirmed by light microscopic observation after connective tissue-specific Masson's trichrome staining after propranolol pharmacokinetic studies. To evaluate the applicability of this method, the pharmacokinetic characteristics of propranolol were examined in the TAA-induced liver fibrotic rat model (male SD rat, 200 to 250 g, SLC, Inc, Japan). Experimental animals were divided into two groups with seven rats; minimal and severe liver fibrotic rats. A 2.0 mg/kg bolus dose of propranolol was administered through tail vein. After restraining the rat by rat restraint cuff, 0.5 ml of venous blood sample was drawn via lateral vein by

heparinized syringe just prior to and at 0.5, 1, 2 and 4 h after propranolol administration and the samples were centrifuged at 2,500 rpm for 10 min and the plasma obtained was frozen at -70°C until analysis. The total plasma propranolol concentration at various time points was analyzed by LC-MS/MS. The initial plasma concentration (C_o) is anticipated to be intercept on the plasma concentration axis when the line is extrapolated back to time zero in the semi-logarithmic concentration-time plot. The area under the plasma concentration-time curve (AUC) was calculated for the total propranolol concentration (C_t) using the linear trapezoidal rule extrapolated to infinity according to a PK Solutions 2.0 (SUMMIT Research Services, Montrose, USA) (Summit Research Services, 2005).

The total area under the first moment-time curve (AUMC) was calculated by integration of time (t) of first moment (C_t•t) (AUMC = C_t•t•dt). Dose/AUC calculated the plasma clearance (CL) (CL = dose/AUC) and the mean residence time (MRT) of the drug in the body was calculated by AUMC/AUC (MRT = AUMC/AUC). The apparent volume of distribution at steady-state (V_{dss}) was calculated by CL•MRT (V_{dss}= CL•MRT) and terminal half-life ($t_{\beta 1/2}$) was calculated by ln2/β (β = slope of the terminal phase). All values presented are expressed as the mean ± SD of seven rats. The pharmacokinetic parameters of the two groups were compared for the statistical differences by independent samples t-test using statistical package for social sciences (SPSS) 20.0 ver. and a probability of $p < 0.05$ was considered significant.

RESULTS

Separation

The molecular structures of propranolol hydrochloride and IS are shown in Figure 1. The simple preparation procedure including the simple liquid extraction of propranolol with acetonitrile and mobile phase and centrifugation of extracted sample and supernatant were directly injected into the isocratic HPLC separation. The chromatograms of (A) double blank plasma, (B) blank plasma with 100 ng/ml of IS, (C) blank plasma with 2.0 ng/ml (LLOQ) of propranolol and 100 ng/ml of IS and (D) rat plasma was taken 2 h after a bolus dose of 2 mg/kg propranolol hydrochloride spiked with 100 ng/ml of IS shown in Figure 2. The retention times of propranolol and IS was about 1.12 and 0.94 min, respectively, that means the potential for the high throughput potential of the proposed method. Blank rat plasma had no significant endogenous peaks at the retention time of propranolol or IS (Figure 2A). To avoid the interference from exogenous/endogenous compounds co-eluted with the target compound, MS/MS (termed tandem MS) detection was performed. Ionization of analytes was carried out using the electrospray ionization (ESI) technique with positive polarity and multiple reactions monitoring (MRM) mode. From full-scan mass spectra via the Q1 mass filter, the protonated molecular ions $[M+H]^+$, at *m*/*z* 260.13 for propranolol and *m*/*z* 264.20 for IS were chosen for the precursor ion (Figure 3A and B). The MS/MS fragmentation was achieved by introducing the $[M+H]^+$ ions into the second quadrupole (Q2) cell with the best collision energy set of 25.0 eV for propranolol and 35.0 eV for IS.

After collision-induced dissociation, the MS/MS transition *m*/*z* 260.13 → *m*/*z* 116.10 for propranolol and *m*/*z* 264.20 → *m*/*z* 58.00 for IS was selected. The most abundant ions in the production mass spectrum at *m*/*z* 116.10 for propranolol and *m*/*z* 58.00 for IS were monitored for quantification (Figure 3A and B).

Method validation

The standard calibration curves showed good linearity within the range of 2.0 to 800 ng/ml using least-squares regression analysis ($y = 0.00101x + 0.000142$, $r^2 \geq 0.999$, $1/x^2$ weighting). Intra- and inter-day precisions and accuracies were determined by analyzing QC samples against a calibration curve on the same day ($n = 5$) and on different days ($n = 5$). As shown in the Table 1, this method allowed good precision and accuracy. The relative standard deviation values of both intra- and inter-day were 0.45 to 8.61% and 0.69 to 5.82%, respectively. Intra- and inter-day accuracies were 97.8 to 106.8% and 100.9 to 108.8%, respectively. Under the described analytical conditions, the LLOQ which is defined as the lowest concentration of propranolol at which both the precision and accuracy were less than or equal to 20% (FDA, 2001), was 2.0 ng/ml.

DISCUSSION

Application in pharmacokinetic study

The mean plasma concentration-time profiles of propranolol after a single bolus dose (2 mg/kg) are illustrated in Figure 4A and the main estimated pharmacokinetic parameters are listed in Table 2. Plasma concentrations of propranolol were in the standard curve range and remained above the LLOQ (2 ng/ml) for the entire sampling period. Because the single bolus dose 4 mg propranolol hydrochloride resulted in a mean plasma concentration of 238.09 ± 96.47 and 439.52 ± 39.74 ng/ml at 0.5 h and 22.42 ± 3.53 and 25.07 ± 8.00 ng/ml at 4 h for the minimal and severe liver fibrosis rat models, respectively, the LLOQ of this method appeared to have enough sensitivity. The sampling schedule should also cover the plasma concentration–time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if area under the curve $(AUC)_t$ covers at least 90% of AUC_∞(Europe, the Middle East and Africa (EMEA), 2010).

Pharmacokinetic characteristics in normal and liver fibrosis groups

In our study, because AUC_t is about 91.3 and 95.5% in the minimal and severe liver fibrosis groups, sampling

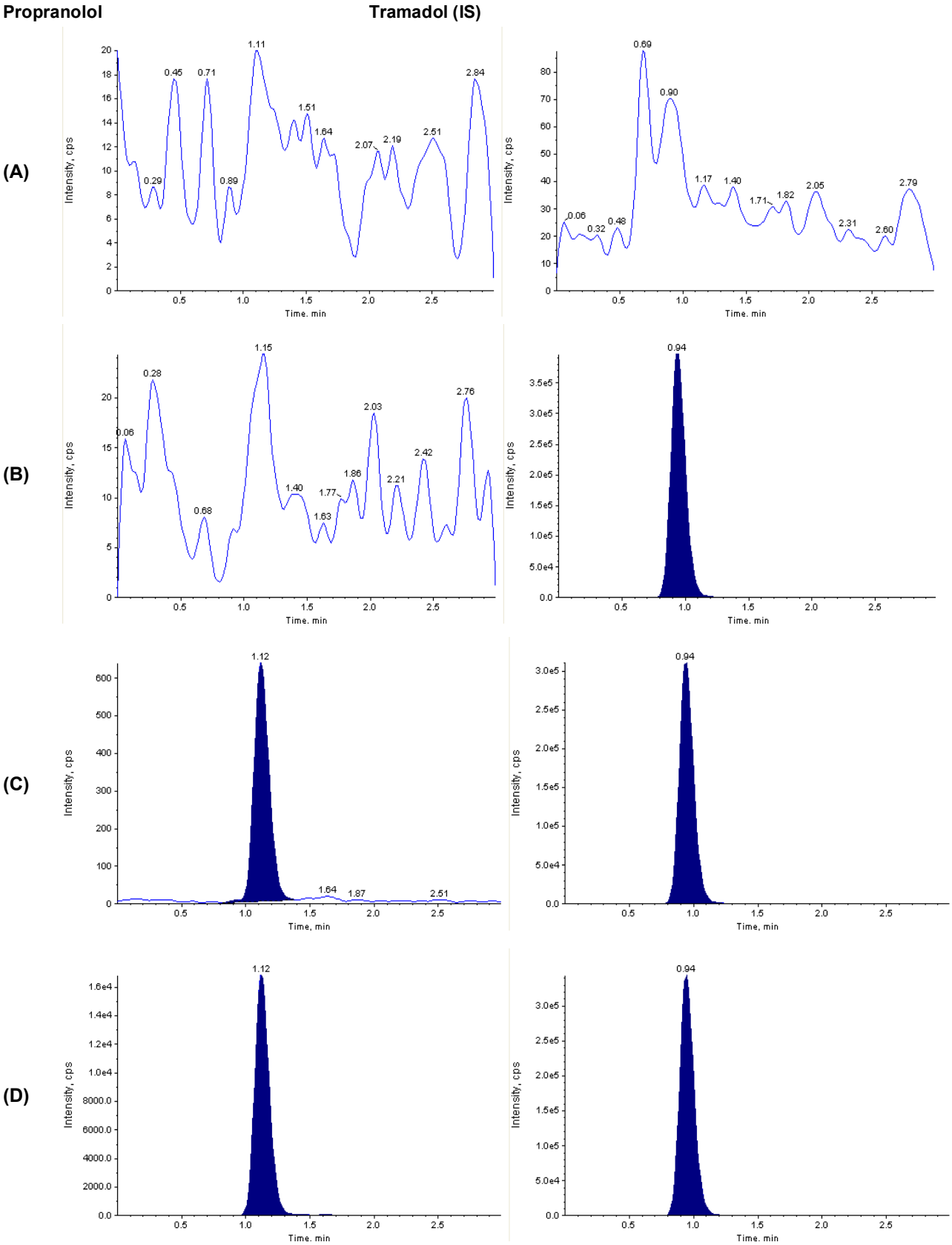


Figure 2. Chromatograms of (A) double blank plasma, (B) with IS (100 ng/ml), (C) with propranolol (LLOQ, 2.0 ng/ml) and IS (100 ng/ml), and (D) rat plasma taken 2 h after a bolus dose (2 mg/kg) of propranolol hydrochloride spiked with IS (100 ng/ml).

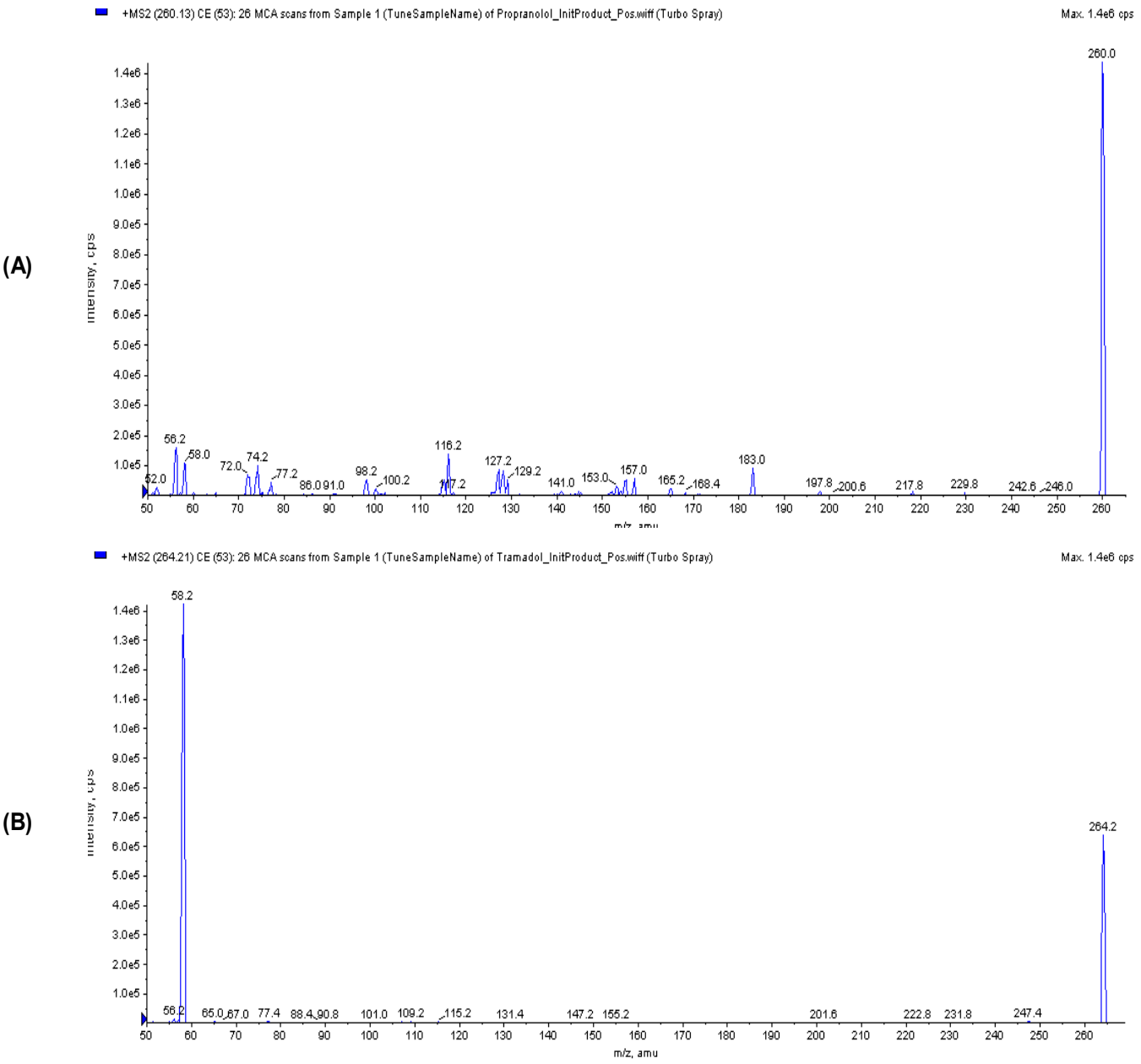


Figure 3. Full-scan mass spectra of precursor and product ions of propranolol; (A) m/z 260.0→116.2 and tramadol (B) m/z 264.2→58.2.

schedule may be enough for pharmacokinetic study. The mean initial plasma concentrations (C_0) and AUC_t of the propranolol of severe liver fibrotic rats, which was dependent on a period of TAA treatment, are significantly increased to 201 and 167.8% of those of minimal liver fibrotic rats shown in Table 2. The mean plasma propranolol concentration-time curves after single bolus dose (2 mg/kg) in the minimal and severe fibrotic rats showed an open two-compartment pharmacokinetic model along with a rapid initial distribution and slower terminal elimination phase that are described in the Figure 4B (Fagan et al., 1982). The plasma profiles of the mean propranolol concentration versus time after a single bolus dose in two groups exhibited marked different patterns and other pharmacokinetic parameters such as AUC, Vd, MRT, elimination rate constant and CL are different between two groups (Table 2). We successfully applied the proposed method to determine propranolol plasma concentration in a preclinical pharmacokinetic study in the TAA-induced hepatic fibrosis rat model as shown in Figure 4C. Therefore, we conclude that this method is proven to be good enough for the determination of propranolol for pharmacokinetic studies using micro-volume of plasma.

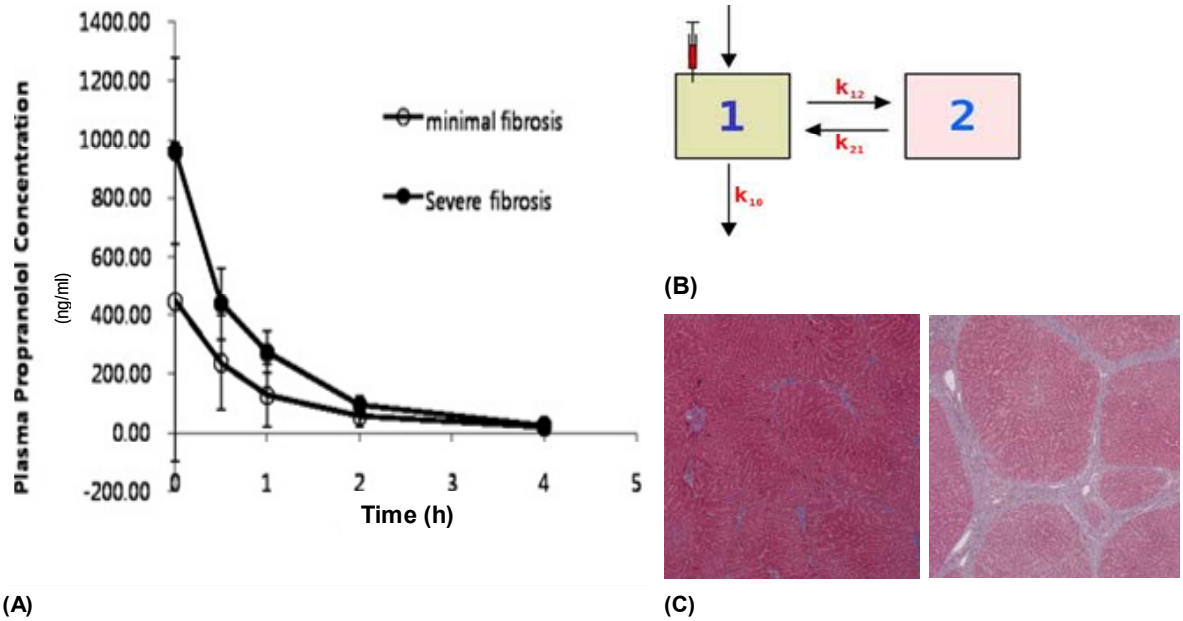


Figure 4. (A) Mean ± SD (n = 7) plasma concentrations vs. time plots after single bolus dose of 4 mg/kg propranolol hydrochloride to the TAA-induced minimal and severe hepatic fibrotic rats, (B) 2-compartment open model (1 = central compartment, 2 = peripheral compartment), k = distribution rat constant and (C) liver light microscopic findings in minimal (left) and severe (right) fibrotic rat, blue = collagen septa, ×40.

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Conflict of interest

Authors reported none.

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Full Length Research Paper

Surfactants solubility, concentration and the other formulations effects on the drug release rate from a controlled-release matrix

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Surfactant effects on the drug release from controlled release systems have been widely studied. These effects are dependent on the surfactant physical properties such as structure, charge, solubility and concentration. In addition, presence of excipients in the matrices can modify the surfactants effects. Here we investigated the effects of surfactant solubility and concentration of excipients on the drug release. Two cationic surfactants (cetrimide and cetylpyridinium chloride), two anionic surfactants (sodium lauryl sulfate and sodium taurcholate) and the amphoteric surfactant betaine were used. The used dissolution medium was simulated gastric fluid pH 1.2. The results revealed that surfactants of the same charge with the drug showed increase of drug release rate in concentration below the surfactant critical micelle concentration (CMC), while the increase in the drug release was to a less extent in surfactant concentration above its CMC. On the other hand, drug release rate was increased with surfactant solubility and vice versa. Surfactants of different charges with that of the drug resulted in a decrease in the drug release rate, depending on surfactant solubility and the excipients. The amphoteric surfactant increased the drug release rate depending on surfactant solubility and concentrations.

Key words: Propranolol hydrochloride, surfactant solubility, controlled-release, surfactant concentration, drug release rate.

INTRODUCTION

The effects of surfactant on the drug release rate have been widely studied. Many of the studies concerned with the surfactant effects on drug release rate from different types of matrices including hydrophilic polymers matrices (Daly et al., 1984; Feely and Davis, 1988; Bolourtchian et al., 2005; Nokhodchi et al., 2008), hydrophobic polymer

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(Efentakis et al.,1990; Bucton et al., 1991; Effentakis et al.,1991; Effentakis et al.,1992) and hydrophilic–hydrophobic polymers (Al- Hmoud et al., 1991; Wells and Parrott, 1992; Al-Hmoud, 2002; Nokhodochi et al., 2002). In a study on the effect of branching on surfactant properties of sulfosuccinates, it was reported that if the micelles are small enough the materials are still considered soluble because the structures are below the size that affects clarity (Olenek and O'lenick, 2007).

It was also reported that deflocculating is one of the mechanisms that accelerate the release rate of the slightly soluble drugs (Schott et al., 1982). It was found that low concentration of the surfactant decrease the surface tension and increase the rate of dissolution, whereas higher surfactant concentration tend to form micelles with the drug and thus reduce the dissolution (Shargel and Yu, 1999). Surfactants are known to solubilize poorly soluble drugs at a concentration above the critical micelle concentration (CMC) as reported before (Mall et al., 1996; Rangel-Yagui et al., 2005). Non-ionic surfactant tween 80 was found to be not a good solvent for the amphoteric poorly soluble drug enrofoxacin, whereas ionic surfactants sodium dodacyl sulfate (SDS) was found to be much better solvent as compared to the cationic surfactant cetyl trimethyl ammonium bromide (CTAB) (Seeder and Agwal, 2009). Very high solubility drug in SDS shows that the non-polar part of the molecule solubilizes into the micellar interior, while the positive charged groups are in the outer core, decreasing the repulsive forces of the head groups of the surfactant molecules, thereby decreasing CMC, increasing the aggregation number and volume of micelles and increasing solubilization.

Much lower solubility in CTAB showed that the orientation of solubilized molecules is such that the negatively charged groups do not take part in solubilization. It was reported in an assessment of solubilization characteristics of different surfactants for carvedilol phosphate (CP) at different pH, it was found that cationic surfactant CTAB and non-ionic surfactant tween 80 were suitable for enhancing the solubility of CP, while the anionic surfactants SDS and sodium taurcholate (ST) were found as solubility retardants (Chacraborty et al., 2009).

Here we aimed to study the effects of surfactant solubility and concentration and the presence of excipients on the drug release. Two cationic surfactants (cetrimide and cetylpyridinium chloride), two anionic surfactants (sodium lauryl sulfate and sodium taurcholate) and the amphoteric surfactant betaine were used.

MATERIALS AND METHODS

Propranolol hydrochloride and sodium lauryl sulphate were kindly donated from Arab Pharmaceutical Manufacturing Co. Ltd. (APM) Jordan. Eudragit RL100 was purchased from Rhom Pharma and cetrimide was kindly donated by the Arab Center for Pharmaceuticals, Jordan. Sodium taurocholate and cetylpyridinium chloride were purchased from Fluka. Betaine was purchased from TCI and magnesium stearate was purchased from BDH chemicals Ltd. NaCMC was purchased from FMC.

Preparation of the tablets

The acrylic resin Eudragit RL100 was powdered and sieved through a 300 µm sieves. Formulations, as listed in Table 1, were prepared to evaluate the release rate of propranolol hydrochloride. The ingredients of each formulation were blended for five minutes in a blender and tablets weighing 400 mg were compressed using a direct compression technique, with a single punch tablet machine (Korch-Erweka). The diameter and the thickness of the tablets were 1 and 0.4 cm, respectively. Tablets were compressed to a hardness level of about 9 kg.

Dissolution study

The United State Pharmacopoeia (USP) basket method (Erweka, DT 6R, Heusenstamm, Germany) was used for all the *in vitro* dissolution studies. Matrices were placed in 900 ml of the dissolution medium and maintained at 37 ± 0.1°C for 8 h at pH 1.2. The rate of stirring was 50 rpm. At appropriate intervals (1, 2, 3, 4, 5, 6, 7 and 8 h), 5 ml of samples was taken and filtered through a 0.45 µm Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The samples were then analyzed by ultraviolet/visible spectrophotometer at wavelengths 289 nm. The mean of three determinations was used to calculate the drug release rate from each of the formulations.

Determination of the critical micelle concentration (CMC) of the surfactants

For the determination the CMC of the different surfactants used in the study, different concentrations of the surfactants were prepared by dissolving these surfactants in distilled water and measuring their surface tension by the DuNoüy ring method using KR-SS Tensiometer.

Data analysis

A model-dependent technique was used to compare the dissolution profiles of the products. The model, based on drug dissolution from dosage forms that do not disaggregate and release the drug slowly, can be represented by the equation:

$$Q/_{Q\infty} = kt^n \quad (1)$$

Where Q is the amount of drug dissolved in time *t,* Q_∞ is the overall released amount of drug in the solution and *k* is the release constant expressed in units of concentration/time and n = 1 in zero order kinetics. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released versus time (Costa and Lobo, 2001; Narashimhan et al., 1999; Hadjiioannou et al., 1993). To characterize the drug release rate in different experimental conditions, $T_{50\%}$ and mean dissolution time (MDT) were calculated from dissolution data

Table 1. Composition of the different formulations matrices used in the study.

Formulation Matrices/Surfactant									
Form.	**Cet.**	**Form.**	**CPC**	**Form.**	**SLS**	**Form.**	**ST**	**Form.**	**Bet.**
F1	0.25	F7	0.25	F13	0.25	F19	0.25	F25	0.25
F2	0.50	F8	0.50	F14	0.50	F20	0.50	F26	0.50
F3	0.75	F9	0.75	F15	0.75	F21	0.75	F27	0.75
F4	1.0	F10	1.0	F16	1.0	F22	1.0	F28	1.0
F5	2.0	F11	2.0	F17	2.0	F23	2.0	F29	2.0
F6	4.0	F12	4.0	F18	4.0	F24	4.0	F30	4.0

Form: Formulations, Cet: Cetrimide, CPC: cetylpyridinium chloride, SLS: sodium lauryl sulfate, ST: sodium taurcholate, Bet: betaine. Each tablet contains 10% RL100, 69% Namco, and 1% MgO, 80 mg of Propranolol HCl and different conc. of surfactants, except for F0 which has no surfactants).

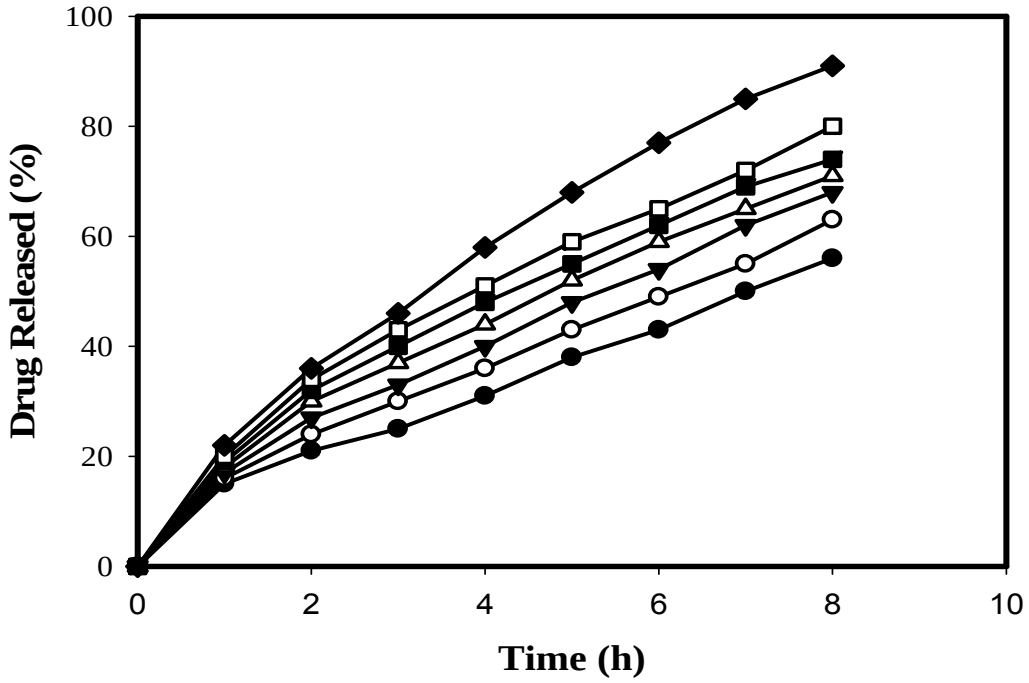

Figure 1. Cetrimide effect on the propranolol-HCl release rate. Cetrimide effect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F1:○, F2:▼, F3: Δ, F4:■, F5:□, F6 :♦) was compared to matrix without surfactant (F0 :●).

according to equations 2 and 3, respectively (Mockel and Lippold, 1993).

$$T_{50\%} = \left(\frac{0.5}{k}\right)^{\frac{1}{n}} \quad (2)$$

$$MT = \frac{n}{n+1} k^{-1/n} \quad (3)$$

The mean dissolution time (MT) is applied to compare the drug release rates. MT is the amount of the drug in the matrix at a given time (n) divide by the initial amount of the drug.

RESULTS AND DISCUSSION

The purpose of the study was to increase the dissolution rate of the poor water soluble drugs by studying the effects of surfactant solubility and concentration and the presence of excipients. Figures 1 and 2 show the increase of the drug release with the increase of cationic surfactants cetrimide and cetylpyridinium chloride, respectively. Increasing cetrimide concentration from 0.25% in F1 to 4% in F6 increased the drug release rate from 1.12 to 1.62%, respectively (Figure 1). Similarly, with cetylpyridinium chloride, increasing its concentration

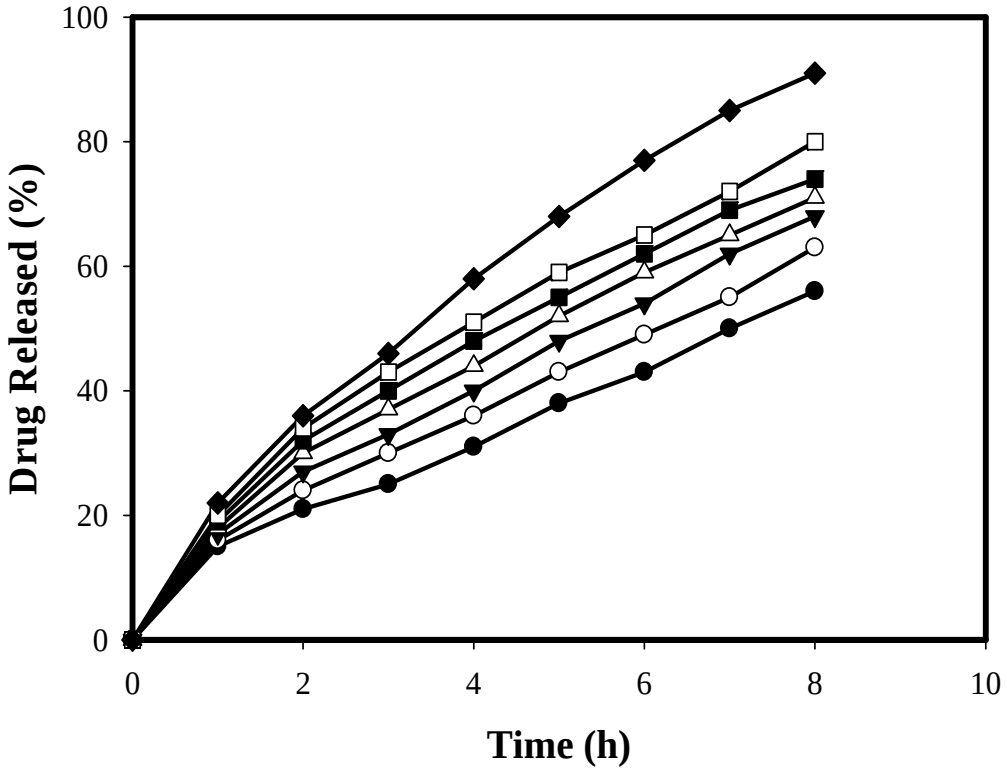

Figure 2. Cetylpyridinium chloride effect on the propranolol-HCl release rate. Acetyl pyridinium chloride effect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F7:○, F8:▼, F9: Δ, F10:■, F11:□, F12 :♦) was compared to matrix without surfactant (F0 :●).

from 0.25% in F7 to 4% in F12 increased the drug release rate from 1.03 to 1.57%, respectively (Figure 2).

This increase can be attributed to many mechanisms. One mechanism relay on the high solubility of cetrimide (Martindale et al., 1996) that forms pores within the matrix resulted in increasing the drug release (Effentakis et al., 1992). Other mechanism explains this increase in the drug release rate due to the repulsive forces between the cationic matrix and cationic drug (Daly et al., 1984; Feely and Davis, 1988; Nokhodochi et al., 2002; Chacraborty et al., 2009). Or, surfactant lowers the interfacial tension between the product and the dissolution medium which increased the release of the drug (Nokhodochi et al., 2002). Increasing the drug release rate with cetrimide was higher than that with cetylpyridinium chloride, at the same concentration, and this can be attributed to the difference of solubility between cetrimide and the solubility of cetylpyridinium chloride (Martindale et al., 1996).

Similarly, Figures 3 and 4 show the fluctuated drug release with the increasing of anionic surfactants sodium taurcholate and sodium lauryl sulfate, respectively. With increasing sodium taurcholate concentration from 0.25 to 0.75% in F13-F15 (below its CMC), there is a decrease in the drug release rate (Figure 3). However, increasing sodium taurcholate concentration from 1.0% in F16 to 4.0% in F18 (above its CMC) increased the drug release rate (Figure 3). In the same manner, sodium lauryl sulfate behave similarly (Figure 4). The decreasing in the drug release rate can be attributed to the formation of complex between the opposite charges of cationic drug and anionic surfactant as reported before (Daly et al., 1984; Feely and Davis, 1988; Noushin et al., 2005; Nokhodchi et al., 2008), or it can be due to increasing the drug entrapment in the colloidal formulated emulsion (Chacraborty et al., 2009). On the contrary, when the concentrations of the surfactant were above the CMC, the formation of surfactant micelles in the dissolution medium helped in increasing the drug release rate (Olenek and O'lenick, 2007; Mall et al., 1996; Rangel-Yagui et al., 2005). The differences in result values between sodium lauryl sulfate and sodium taurcholate was attributed to solubility differences between them (Effentakis et al., 1992; Martindale et al., 1996).

With amphoteric surfactant, betaine, increasing surfactant concentration from 0.25% in F25 to 4.0% in F30 increased the drug release rate (Figure 5). This increase in the drug release rate can be attributed to it;

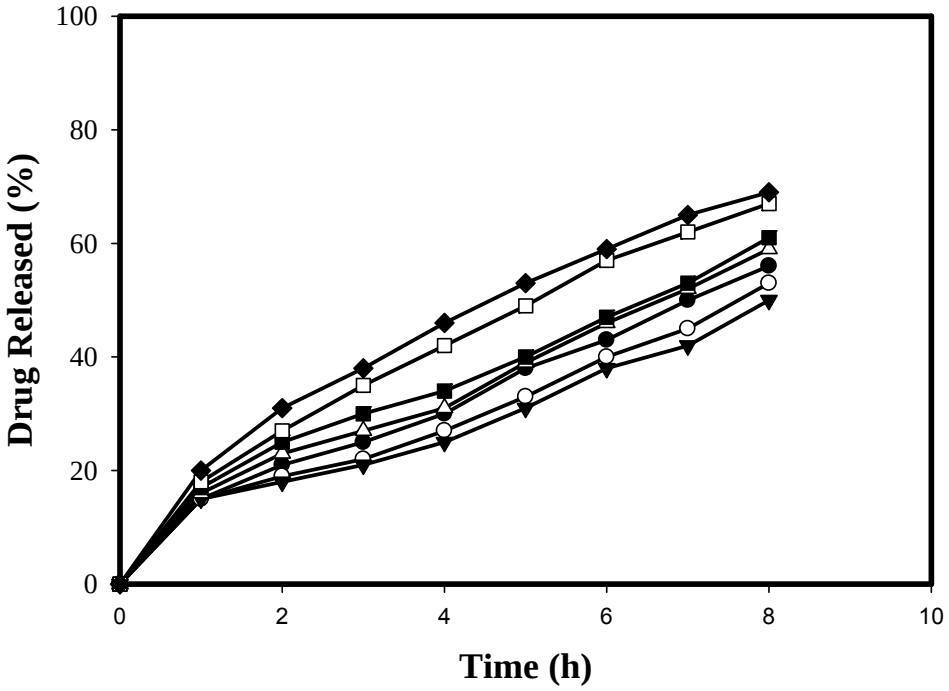

Figure 3. Sodium lauryl sulfate effect on the propranolol-HCl release rate. Sodium Laurayl sulfateeffect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F13:○, F14:▼, F15: Δ, F16:■, F17:□, F18 :♦) was compared to matrix without surfactant (F0 :●).

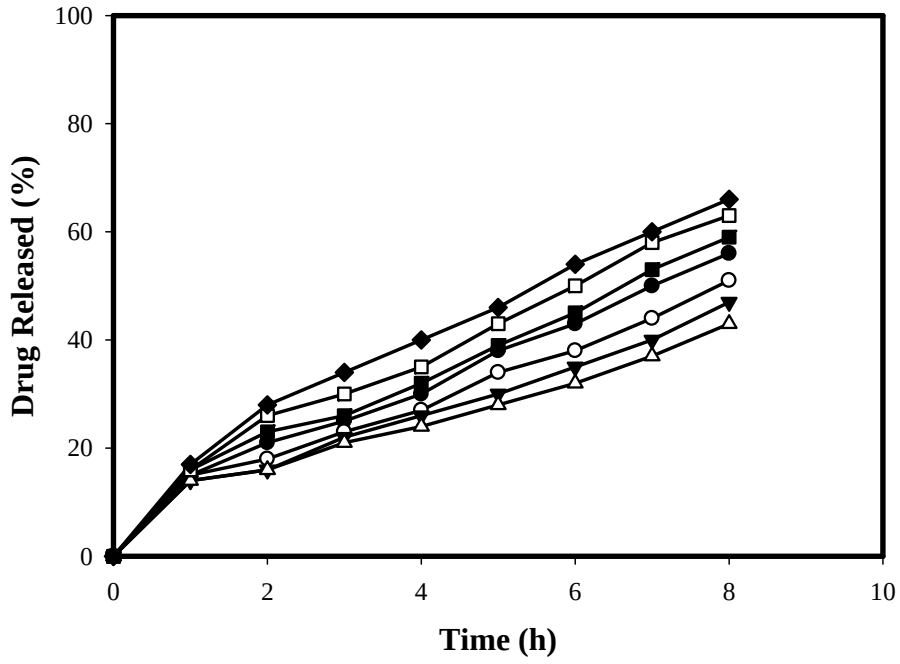

Figure 4. Sodium taurcholate effect on the propranolol-HCl release rate. Sodium taurcholateeffect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F19:○, F20:▼, F21: Δ, F22:■, F23:□, F24 :♦) was compared to matrix without surfactant (F0 :●).

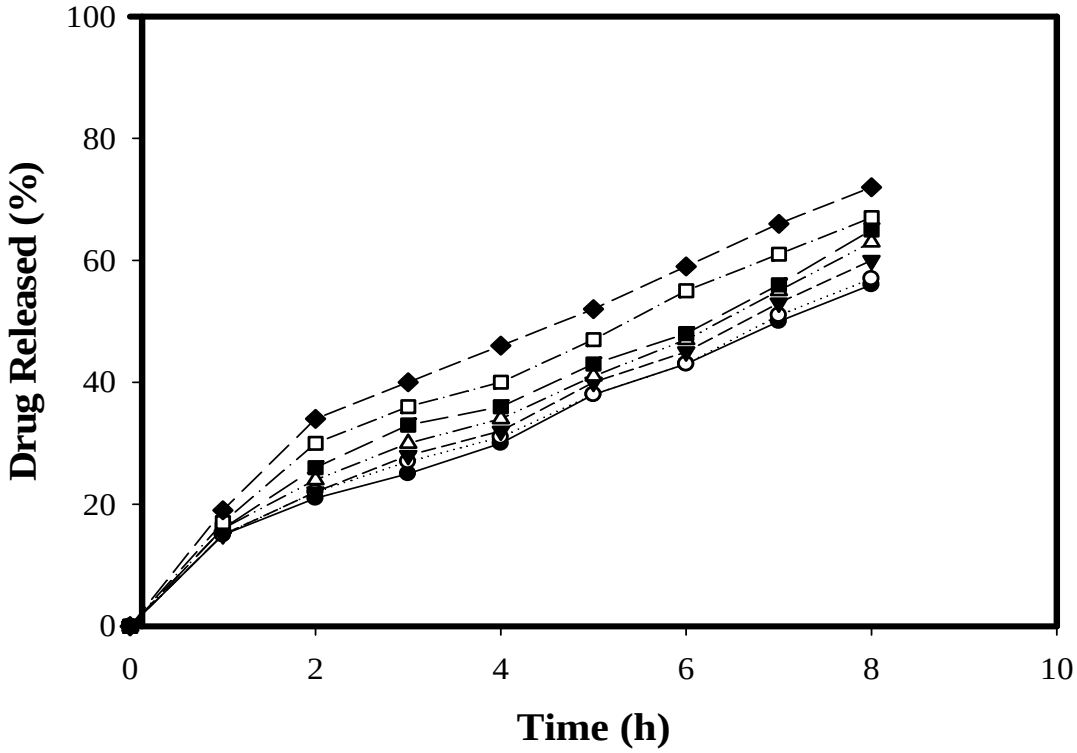

Figure 5. Betaine effect on the propranolol-HCl release rate. Betaine effect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F25:○, F26:▼, F27: Δ, F28:■, F29:□, F30 :♦) was compared to matrix without surfactant (F0 :●).

Table 2. Surface tension values of surfactants at different concentrations.

Conc.	Formulation matrices/surfactant									
	Cet.	±SD	CPC	±SD	SLS	±SD	ST	±SD	Bet.	±SD
0.25	47	2.12	47	1.01	56	1.1	54	1.64	55	1.95
0.5	43	1.10	43.5	0.95	52	0.9	50	1.15	52	0.92
0.75	40	0.95	39	1.1	47	1.2	42	0.09	48	1.35
1.0	40	0.09	36	0.91	44	0.51	42	0.01	43	0.77
2.0	40	0.01	36	0.03	45	0.6	42	0	36	0.43
4.0	40	0	36	0	44	0	42	0	36	0

Cet: Cetrimide, CPC: cetylpyridinium chloride, SLS: sodium lauryl sulfate, ST: sodium taurcholate, Bet: betaine. Surfactants (Cetrimide, Cetylpyridinium, Sod. Lauryl sulfate, Sod. Taurcholate and betaine) used at concentrations (0.1, 0.25, 0.50, 0.75, 1.0 and 2.0). CMC of the surfactant were approximately at the concentrations as follows: SLS = 0.75%, ST =0.5%, Cet. = 0.5%, CPC = 0.75% and Bet. = 1%.

increasing surfactant concentration leads to increasing the aggregation number and volume of the micelles and increasing solublisation (Seedher and Agwal, 2009). All results were conducted to the regression analysis as shown in Table 2. All the r^2 values were higher than 0.985, indicating that the drug release rate followed zero order kinetics (Table 3).

Time required for 50% drug release ($T_{50\%}$) and mean dissolution time (MDT) were calculated from dissolution data and presented in Table 4. The MDT value was found

Table 3. Kinetics of the drug release rates.

Formulation	Correlation coefficient	Slope	Intercept	Formulation	Correlation coefficient	Slope	Intercept
F0	0.998567	0.169897	8.464286	F16	0.994129	0.240628	8.392857
F1	0.999643	0.161113	8.964286	F17	0,993455	0.241649	7.035714
F2	0.999308	0.153073	10.14286	F18	0.993652	0.262458	7.071429
F3	0.998397	0.141199	11.60714	F19	0.99529	0.172636	7.678571
F4	0.996053	0.139361	12.71429	F20	0.992102	0.181312	7.321429
F5	0.992785	0.138217	14.03571	F21	0.986849	0.190688	7.142857
F6	0.9919	0.137741	15.35714	F22	0.989363	0.208686	7.392857
F7	0.999462	0.168832	9.75	F23	0.988574	0.212672	6.571429
F8	0.999387	0.16134	0.16134	F24	0.989342	0.233577	6.892857
F9	0.999472	0.153966	11.17857	F25	0.996456	0.168496	8.607143
F10	0.9937	0.149182	13.46429	F26	0.998885	0.1721	8.785714
F11	0.990853	0.145194	14.57143	F27	0.998189	0.167392	8.964286
F12	0.990325	0.139395	14.71429	F28	0.99449	0.164509	8.821429
F13	0.994673	0.178726	7.964286	F29	0.998103	0.165052	9.464286
F14	0.995423	0.191781	8.0	F30	0.998538	0.162315	9.607143
F15	0.994911	0.211034	7.642857	-	-	-	-

Correlation coefficient (r^2) for the formulation from F0 to F30, the values of (r^2) for these formulations were greater than 0.985, indicating drug release follows zero- order kinetics.

Table 4. $T_{50\%}$ and MDT for different formulations.

Formulation	$T_{50\%}$ (h)	MDT	Formulation	$T_{50\%}$ (h)	MDT
F0	5.49	6.38	F16	6.47	10.58
F1	6.11	7.11	F17	5.17	7.55
F2	5.38	5.94	F18	4.46	6.73
F3	4.70	4.99	F19	5.56	6.42
F4	3.27	3.19	F20	6.58	7.23
F5	3.90	3.96	F21	6.92	9.23
F6	3.33	3.29	F22	7.81	11.93
F7	6.22	7.46	F23	8.51	13.80
F8	5.37	6.01	F24	9.01	17.09
F9	4.71	5.13	F25	6.88	8.47
F10	4.38	4.59	F26	6.55	8.02
F11	3.86	3.93	F27	6.42	7.76
F12	3.34	3.34	F28	6.20	7.34
F13	7.61	10.08	F29	5.43	6.22
F14	7.99	11.28	F30	4.65	5.03
F15	6.62	9.45	-	-	-

MDT: mean dissolution time.

shown in Table 2. All the r² values were higher than 0.985, indicating that the drug release rate followed zero order kinetics (Table 3).

Time required for 50% drug release ($T_{50\%}$) and mean dissolution time (MDT) were calculated from dissolution data and presented in Table 4. The MDT value was found

to be a function of surfactant type and its concentration. Lower MDT indicates a higher dissolution rate of the formulation.

Conclusion

The process of drug release from matrices involves many routes each to a varying extent, depending on the properties of the drug, as well as the polymer of matrices and additives such as surfactants. According to our results, the presence of the surfactants has an important role on the drug release rate improvement. The extent of drug release rate improvement relays on the physic-chemical properties such as concentration and solubility of surfactants.

ABBREVIATIONS

Cet, Cetrimide; **CPC,** cetylpyridinium chloride; **SLS,** sodium lauryl sulfate; **ST,** sodium taurcholate; **Bet,** betaine; **Form,** formulation; **CMC,** critical micelle concentration; **MgO,** magnesium oxide.

Conflict of interest

Authors reported none.

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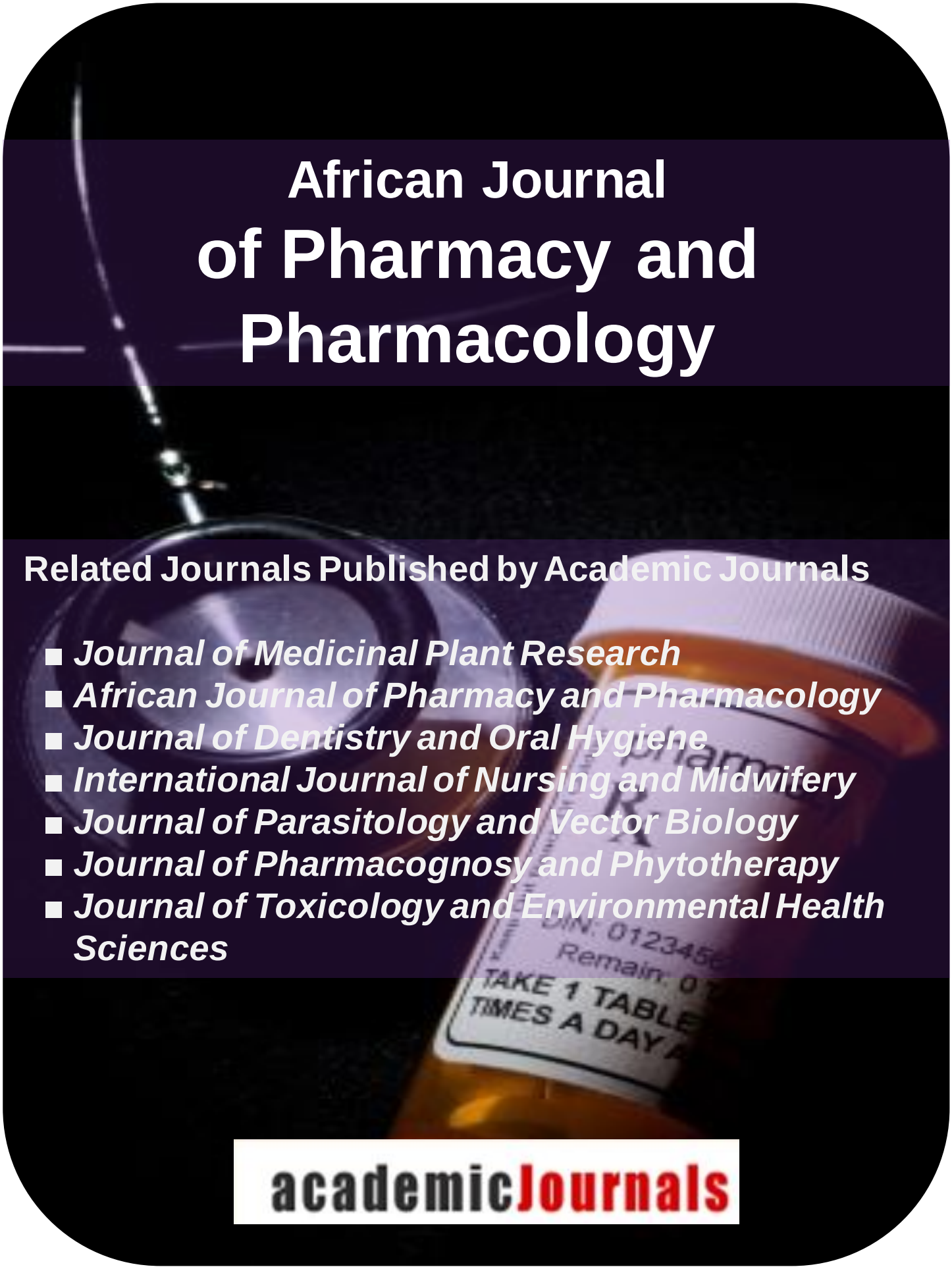

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