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SHORT COMMUNICATION article

Pre-formulation solubility study of praziquantel in different media and solubilizing agents using the saturation shake-flask method

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Abstract: Praziquantel is a medication used to treat schistosomiasis. It has low bioavailability due to poor solubility in water and common solvents, resulting in its availability only in a solid dosage form. This study is aimed to enhance the solubility of praziquantel by the use of various solubilizing agents. The solubility evaluation was conducted using the shake-flask method. The solvents were; buffered phosphate pH 7.4, 0.5% propylene glycol in buffered phosphate pH 7.4, 0.2% tween 80 in buffered phosphate pH 7.4, 30% methanol in buffered phosphate pH 7.4, and assessment of the solubility of the drug in 0.1 N hydrochloric acid, 0.2% sodium lauryl sulfate, and a mixture of 0.2% sodium lauryl sulfate in 0.1 N hydrochloric acid. The solubility of praziquantel was determined at a temperature of 37±2°C, and the concentrations were detected by high-performance liquid chromatography at λ=210 nm. The results show that the solubility of praziquantel was 124.3±2 µg/ml in 30.0% methanol in buffered phosphate pH 7.4, 100.6±2 µg/ml in 0.2% tween 80 in buffered phosphate pH 7.4, 112.4 µg/ml in 0.1 N hydrochloric acid, 370.29 µg/ml in 0.2% sodium lauryl sulfate, and 278.7 µg/ml in a mixture of 0.2% sodium lauryl sulfate in 0.1 N hydrochloric acid (pH 2). Thus, praziquantel can be considered a highly soluble drug in 0.2% sodium lauryl sulfate. Other surfactants may improve the solubility of such poorly soluble drugs.

Introduction

Praziquantel (PZQ) is a medication used to treat various parasitic infections, including schistosomiasis, liver flukes, and tapeworm infections [1]. PZQ is included in the World Health Organization (WHO) model list of essential drugs [2]. PZQ is practically insoluble in water and has poor bioavailability [3]. It is only available in a solid dosage form (tablets). However, the potential exists to formulate it into other dosage forms if sufficient aqueous solubility could be achieved. In previous studies, researchers have focused on improving PZQ properties by preparing solid dispersions of the drug with povidone [4], sodium starch glycolate [5], and by preparing PZQ-cyclodextrins systems [6-11], PZQ-liposomes systems [12], polymeric and solid lipid nanoparticles [13-16], fast dispersible granules [17], and more recently PZQ-lipid nanocapsules [18]. Solubility is critical because it

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estimates the poorly defined drug substance serves its pharmacological and toxicological profiling, and it is a frequently encountered challenge in screening studies of New Chemical Entities (NCE) and formulation design and development. According to the International Union of Pure and Applied Chemistry (IUPAC), solubility may be defined as the analytical Composition of a saturated solution expressed in terms of the proportion of a designated solute in a designated solvent and the solubility of that solute. It is described as a concentration, molality, mole fraction, mole ratio, etc. [19].

There are various techniques available to improve the solubility of poorly soluble drugs. A conventional approach is by using surfactant, a wide variety of surfactants like tweens, spans, polyoxyethylene glycerides, polyoxyethylene stearates, and synthetic block copolymers, etc. are very successful as excipients and carriers for dissolution enhancement [20]. Surfactants are unique substances with hydrophobic and hydrophilic properties, allowing them to adsorb at the interfaces of liquids, solids, and gases. They can form self-associated clusters, leading to organized molecular assemblies such as monolayers, micelles, vesicles, and membranes. By reducing surface tension, they can easily mix or disperse as emulsions in water or other liquids [21]. Anionic surfactant sodium lauryl sulfate (SLS or sodium dodecyl sulfate, SDS) and nonionic surfactant tween 80 (polysorbate 80) are widely used in various drug dosage forms to regulate wetting, stability, and solubilization of hydrophobic drugs [22]. Another effective technique to enhance the solubility of sparingly soluble drugs is using of co-solvents. Various co-solvents, such as polyethylene glycol (PEG), glycerin, and ethanol [23], can address the issue of low solubility in sparingly soluble drugs. Propylene glycol (PG) is a synthetic co-solvent added to numerous drug formulations to enhance solubility [25]. PG is a water-soluble alcohol commonly used as a solvent in many intravenously administered drugs in the intensive care unit and general medicine ward to overcome the low solubility of sparingly soluble drugs. While chemically and physiologically similar to ethylene glycol, it is notably less toxic and therefore designated by the FDA as generally recognized as safe (GRAS) for use in food [24, 25].

Other techniques to improve drug solubility include particle size reduction, the adjustment of micro-environmental pH, and, the addition of a water-miscible solvent in which the drug has good solubility known as co-solvents, solid dispersion, nano-crystallization, nano-suspension, hydrotrophy, complexation, self-emulsifying drug delivery systems [26]. This study aimed to assess the solubility of PZQ in phosphate buffer solutions and hydrochloric acid (HCL) media, both alone and with the addition of various solubilizing agents. The primary purpose of pre-formulation testing is to provide formulators with valuable information to develop stable and bioavailable dosage forms that can be manufactured on a large scale. Furthermore, a drug requires a certain level of solubility in water to enter the bloodstream and produce a therapeutic effect [27].

Materials and methods

Evaluation of the solubility of PZQ using the shake-flask method: All the solubility experiments were carried out using the shake-flask method [28]. Saturated solutions were prepared by adding an excess of PZQ powder into screw-capped vials containing 10.0 ml of the following media: buffered phosphate (BPS) pH 7.4, 0.5% PG in buffered phosphate pH 7.4, 0.2% tween 80 in buffered phosphate pH 7.4, 30% methanol in buffered phosphate pH 7.4, and assessment of the solubility of the drug in 0.1 N HCL, 0.2% SLS, and a mixture of 0.2% SLS in 0.1 N HCl. The mixtures were shaken for 24 hrs in a thermostatically controlled shaking water bath at 100 strokes/min at 37ºC, and incubated for another 24 hrs at the same temperature. Once the equilibrium was attained, the agitation was stopped and the solution was kept still for 1.0 hr. The mixtures were then filtered through a 0.45-µm millipore filter.

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High-Performance Liquid Chromatography (HPLC) analysis of PZQ filtered samples: The PZQ concentration in filtered samples was determined by HPLC analysis at λ 210 nm. The HPLC analysis showed that PZQ did not decompose during the time of solubility measurement in all solvents. Each solubility value is an average of three measurements, simultaneously with the respective standard deviations. The solubility of PZQ was calculated based on standard calibration curves. Quantitative HPLC was performed on HPLC-1260 Infinity Agilent technologies equipped with an isocratic pump, a variable wavelength UV/Vis detector, and a manual injector, injection valve with a 20 µL loop on a reversed-phase column C18 (Column: packing Egusil BDS-C18) with a particle size of 5 µm 250×4.6 mm and Guard column. The contents of the mobile phase were acetonitrile and water, a ratio of 70: 30, the mobile phase was filtered through a membrane filter (0.45 µm x 47 mm) and degassed using an ultrasonic bath for 30 min. The analysis required less than nine min. The flow rate of the mobile phase was isocratic at 1.0 mL/min. The HPLC system was operated at 30.0±1.0°C. And column temperature was maintained at ambient. The volume of injection was 20 µl, and the eluent was detected at λ=210 nm.

Results

The solubility of PZQ in different media and solubilizing agents was measured and the results are shown in **Table 1**. Under the optimized chromatographic conditions applied, sharp symmetric peaks were obtained for PZQ with a retention time of 5.0 min **(Figure 1)**. Linearity was checked in the 0.5 to 25 µg/ml concentration by plotting the peak area against PZQ concentration. A determination coefficient (r^2) of 0.999 indicated a good correlation between peak area and drug concentration within the concentration range tested. The PZQ calibration graph in acetonitrile (ACN) is shown in **Figure 2**. The detection and quantitation limits were 0.37 µg/ml and 1.13 µg/ml, respectively. The relative standard deviation of responses RSD (%) in the analysis of replicate quality control samples containing known concentrations of analytes (5,10, and 15 µg/mL) was calculated to represent precision and accuracy, respectively. The intra-day RSD (%) for three quality control was 6.27% and inter-day precision was 1.44%, which were all below 12.7%, which is quite acceptable for an accurate and precise validated HPLC method [28]. The validated method was used to determine the concentration of PZQ.

Table 1: Praziquantel solubility in different media and solubilizing agents

Medium	Solubility (µg/mL)
Phosphate buffer pH 7.4	70.0±2.0
30% Methanol in Phosphate buffer pH 7.4	124.3±2.0
0.2% Tween 80 in Phosphate buffer pH 7.4	100.6±2.0
0.5% Propylene glycol in Phosphate buffer pH 7.4	90.3±2.0
0.1 N HCl (pH 2)	112.40
0.2% SLS in 0.1 N HCl (pH 2)	278.70
0.2% SLS solution	370.29

Praziquantel is sparingly soluble in water at 25°C (0.40 mg/mL) between pH 1.0 and 7.5 [29]. Thus, this study showed the lowest solubility in phosphate buffer pH 7.4 (70.0±2.0 µg/mL) and in 0.1 N HCl (pH 2) (112.40 µg/mL). The addition of 0.2% SLS in 0.1 N HCl (pH 2) and 0.2% tween 80 in phosphate buffer pH 7.4 increased the solubility of the drug to 278.70 µg/mL and 100.6±2.0 µg/mL, respectively, **Figures 3** and **4.** The anionic surfactant SLS showed a remarkable solubilizing ability, with the highest solubility achieved using 0.2% SLS in water, at 370.29 µg/mL **(Figure 4)**.

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PZQ is highly hydrophobic with a Log P of 2.7 [30], however, it is soluble in ethanol (97.0 mg/mL) [31]. When methanol and PG were added as cosolvents by 30.0% and 0.5%, respectively to phosphate buffer, the solubility of PZQ increased. The addition of methanol increased solubility to 124.3±2.0 µg/mL compared to phosphate buffer alone (70.0±2.0 µg/mL), while PG increased solubility to 90.3±2.0 µg/mL.

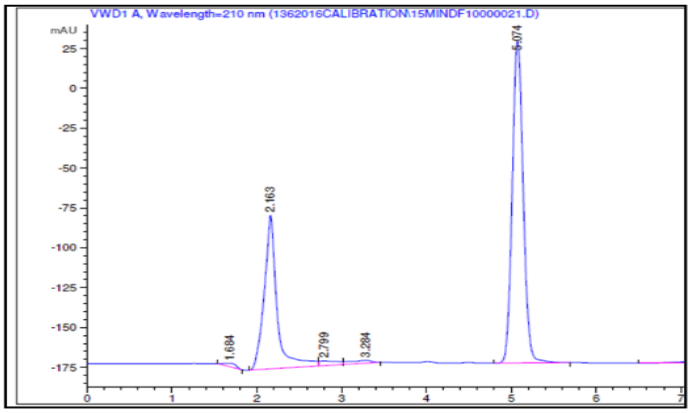

Figure 1: HPLC chromatograms of praziquantel 25 µg/mL in acetonitrile at λ_{max} 210 nm

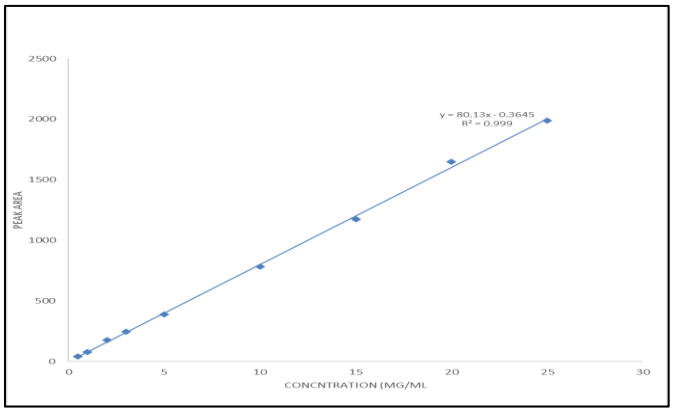

Figure 2: Calibration curve of praziquantel by HPLC in acetonitrile at λ_{max} 210 nm

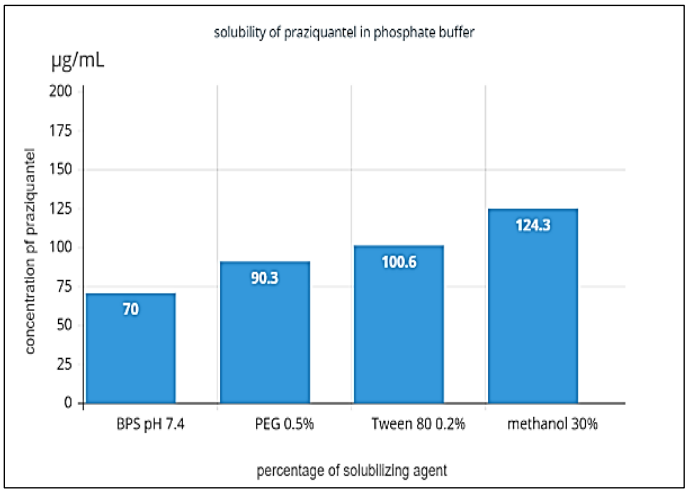

Figure 3: Solubility of praziquantel in phosphate buffer pH 7.4 and 5.0% PEG, 0.0.2% T80 and 30.0% methanol

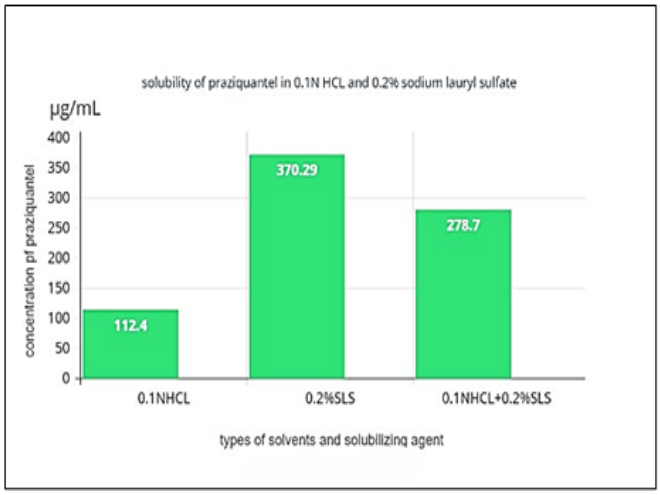

Figure 4: Solubility of praziquantel in 0.1 N HCL, 0.2% SLS and 0.2% SLS in 0.1 N HCL

Discussion

The solubility of PZQ is a crucial factor to consider, as it is insoluble in water and only slightly soluble in common solvents. Solubility data were collected to select an appropriate medium for drug release studies. The current study demonstrated that the use of surfactants, such as tween 80 and SLS improved the solubility of PZQ. It is well-known that surfactants can enhance the dissolution of poorly water-soluble drugs by either reducing the surface tension at the solid drug's surface, which increases the available area for dissolution, or by directly increasing the solubility of the drug [32]. The increase of PZQ solubility after the addition of methanol and PG is in line with a previous study [33], which showed that methanol, ethanol, and other compounds, are used as cosolvents for the extraction of steroidal drugs, improving solubility by up to 75.0% [34]. The role of cosolvents is to change the polarity of the solvent by interaction with the matrix or interaction with the analyte. Therefore,

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the increase in solubility of PZQ is due to the increase in solvent density or intermolecular interactions between the cosolvent and the solute. The results indicate that the type of solvent and solubilizing agent used can greatly affect the solubility of PZQ, which is important for creating effective drug delivery systems. Solvents that contain SLS showed good solubilizing properties for PZQ, indicating the potential for enhanced bioavailability and effectiveness in formulations with SLS.

Conclusion: The solubility evaluation provided insights into the solubility profile of PZQ in various solvents and can guide formulation strategies to improve the bioavailability and efficacy of PZQ in pharmaceutical products. The solubility of PZQ varied significantly among the different solvents tested. Adding solubilizing agents such as methanol, tween 80, PG, and 0.2% SLS enhanced the solubility of PZQ.

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Author contribution: ROA conceived & designed the study, and collected the data. NMB contributed data analysis tools. ROA & NMB performed the analysis/interpretation of data. NMB drafted the manuscript/revised it for important intellectual context. Both authors approved the final version of the manuscript and agreed to be accountable for its contents.
Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission were completely observed by the authors.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.