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RESEARCH ARTICLE

SALTING COEFFICIENT AND THERMODYNAMIC PARAMETERS OF HALOFANTRINE IN ELECTROLYTES AND AQUEOUS CO-SOLVENT SYSTEMS

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ABSTRACT

The study was to examine the solubilization behaviour of halofantrine in electrolytes and co-solvent systems in order to select additive(s) for development of the drug into matrix and structured delivery devices. Solubility of halofantrine was determined by adding excess of the drug in 50 mL of double distilled water, electrolytes (NaCl, Na_2SO_4, $NaNO_3$, Na_2CO_3) solution (0.01 – 0.50 M), co-solvents (10, 20, 40, 80 % v/v) of glycerol, polysorbate 80 and propylene glycol, in a 100 mL capped conical flask at 25 and 40 ºC respectively, equilibrated for 48 h and solubility determined spectrophotometrically from a validated standard curve (5-50 µg/mL, r^2=0.9998) at 290 nm. Results showed that solubility of halofantrine was dependent on temperature and nature of additive(s). Only NaCl and polysorbate 80 improved solubility of halofantrine significantly with a negative K_s, ΔG_{trans} and positive ΔH^o_{trans}, ΔS_{trans} values at all concentration and temperature showing the spontaneity of solubilization; others salted-out halofantrine with higher K_s, ΔG_{trans}, ΔH^o_{trans} and negative ΔS_{trans} providing a less thermodynamically favourable environment for halofantrine solubilization. The Setschenow and thermodynamic parameters of transfer obtained could be utilized for development of halofantrine into structured devices and matrices to achieve efficient loading and entrapments that would improve solubility, absorption and bioavailability.

INTRODUCTION

One major limitation with the design of oral dosage forms of drugs lies with their poor bioavailability as a result of poor permeability and solubility of drugs (Edward and Li, 2008). The effects of poor aqueous solubility include the high dose of drug required to attain the plasma concentration level, drug development challenges for formulation scientists (Sharma *et al*., 2009), poor absorption, insufficient solubility for intravenous dosing and gastrointestinal tract toxicity due to frequent high dose administration. Halofantrine is a substituted phenanthrene, chemically designated as 1,3-dichloro-α-[2-(dibutylamino)ethyl]-6-trifluoromethyl-9-phenanthrene methanol. It is effective against mutating resistance *Plasmodium falciparum* malaria (Nelson, 2006) and study has shown that halofantrine binds to hematin *in-vitro* (Friedman and Caflisch, 2009) or to plasmepesin, a hemoglobin degrading enzyme unique to malaria parasites (Liu, 2006) suggesting the possible mechanisms of action. It is a lipophilic compound with partition coefficient 3.20±0.04 (confirming the lipophilicity) and half-life of 4 days. Various techniques to improve drug solubility such as chemical and physical modifications have been reported (Jain *et al*., 2010; Seedler and Aggarwal, 2009; Jason *et al*., 2012; Patel *et al*., 2012; Das *et al*., 2011; Samy *et al*., 2010; Ghareeb *et al*., 2009; Abdul-Fattah and Bhargava, 2002; Liversidge and Conzentino, 1995; Moschwitzer *et al*., 2004; Vogt *et al*., 2008) but these approaches did not account for the effects of small concentrations of additives (inorganic electrolytes) on solubility and activity coefficient of drugs. Alternative approach (which improves solubility, absorption and bioavailability with minute additives) involves the use of Setschenow parameters to describe the ability of additives (electrolytes) to salt-in or salt-out drugs in additives. The addition of an electrolyte to a solution of drug can cause salting in or salting out of the latter which has been described by many theories (Sugunan and Benny, 1995). Due to life threatening cardio toxic effects of halofantrine as a result of unpredictable and erratic absorption and the increasing reports of halofantrine treatment failures associated with incomplete absorption (Schuster, 2006), we undertook this study with a view to improving the solubility, absorption and bioavailability of halofantrine using inorganic salts and co-solvents which are known to modify the thermodynamic parameters of dissolution of molecules in order to design a better formulation of halofantrine capable of alleviating cardio toxic and other dose related effects by maintaining predictable absorption profile for orally administered or other suitable forms of administration.

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MATERIALS AND METHODS

Materials

UV spectrophotometer (Jeenway, 6305, England), thermostatic water bath (UNISCOPE SM 801A, England), Electrical weighing balance (310g.OHAUS Coporation, USA), Halofantrine (Glaxosmithklime, South Africa). All other chemicals and reagents were of analytical grade; and were used without purification.

Methods

Preparation of Salt and Cosolvent Solutions

The following electrolytes were used for the studies-sodium chloride, sodium sulphate, sodium carbonate and sodium nitrate. Each salt was prepared at molar strengths of 0.01 to 0.50 by weighing appropriate quantity of salts and dissolving in double distilled water. The aqueous co-solvents used- polysorbate 80, glycerol and propylene glycol were prepared by homogeneous mixing with double distilled water at strengths of 20, 40, 60, 80, and 100 % v/v.

Determination of Solubility

The solubility of halofantrine was determined in triplicate by adding excess drug to 50 mL each of the electrolytes, co-solvents and double distilled water in a 100 mL capped conical flask at temperatures of 25 ºC and 40 ºC. The solutions were equilibrated in a thermostatic water bath at 100 rpm for 48 hours at both temperatures. The temperature uniformity within the water bath was maintained at ±0.5 ºC.

Halofantrine Assay

The equilibrated solution was centrifuged for 30 minutes. An aliquot of each of the sample solutions was filtered using a 10 mL syringe attached to a 0.5 µm Millipore filter into empty test tubes pre-equilibrated to the experimental temperatures to reduce effect of temperature on solubility, suitably diluted and assayed spectrophotometrically for halofantrine against appropriate blanks at maximum wavelength of 290 nm. The solubility was calculated from the pre-calibrated standard curve. The calibration curve (absorbance verses halofantrine concentration) was constructed by measuring standard solutions of halofantrine for every series of samples. Validation of the method was performed to ensure that the calibration curve between 5 and 50 µg/ml was in the linearity range of the assay and the coefficients of variation were less than 2 % both intra-day and inter-day. The Setschenow parameter (K_s) and the thermodynamic parameters of transfer (ΔH_{trans} and ΔS_{trans}) of halofantrine from water to salt or cosolvent solutions were computed from solubility data at 25 ºC and 40 ºC using equations 1-3 respectively (Sugunan and Benny, 1995).

$$[Salt].K_s = Log[S_o/S] \quad \text{---------Equation 1}$$

where S_o is the solubility of halofantrine in absence of salt or cosolvent, S is the solubility of halofantrine in presence of salt or co-solvents.

$$\Delta G_{trans} = RT \ In \ K_s \quad \text{---------Equation 2}$$

where ΔG_{trans} is the standard Gibb's free energy change.

$$T\Delta S_{trans} = \Delta H_{trans} - \Delta G_{trans} \quad \text{-------Equation 3}$$

where ΔH_{trans} and ΔS_{trans} are thermodynamic parameters for one mole of halofantrine from water to salt or cosolvent solutions (0.1 M) at 25 ºC. Van't hoff reaction isochore was applied to K_s to estimate the ΔH_{trans} at different temperatures (25 ºC and 40 ºC). The ΔH_{trans} involved was estimated from the equation (Etman and Naggar, 1990) represented as:

$$\Delta H_{trans}=2.303\log[\{(S/S_o)_{40\,^oC}/(S/S_o)_{25\,^oC}\}.\{(RT_2T_1)/(T_2-T_1)\}] \quad \text{----Equation 4}$$

where T_1 and T_2 are 298.15 K and 313.15 K respectively

RESULTS

Table 1 showed the solubility of halofantrine in double distilled water, and different concentrations of electrolyte and co-solvent solutions at temperatures of 25 ºC and 40 ºC while Table 2 represented the thermodynamic parameters of transfer of halofantrine from double distilled water to salt or co-solvent solution.

Table 2. Setschenow parameter (K_s) and Thermodynamic Parameters of Transfer of Halofantrine at 25 ºC.

Salt/Cosolvent	Ks	ΔG_{trans} (KJmol^{-1})	ΔH_{trans} (KJmol^{-1})	ΔS_{trans} (JK^{-1}mol^{-1})
Sodium chloride	0.240	594.917	10.779	-1.960
Sodium nitrate	0.100	247.882	10.762	-0.796
Sodium sulphate	-0.057	-141.293	10.831	0.510
Sodium carbonate	0.120	297.458	10.687	-0.962
Polysorbate 80	-0.015	-37.182	10.832	0.161
Propylene glycol	0.010	24.788	10.794	-0.047
Glycerol	0.040	99.153	10.860	-0.296

Figures 2a-d showed the log linearity plot of halofantrine solubility data, from where the thermodynamic data were generated. The results showed that all the additives affected the solubility and thermodynamics of solubilization of halofantrine depicting the dependency of solubilization on nature of additive(s) and temperature.

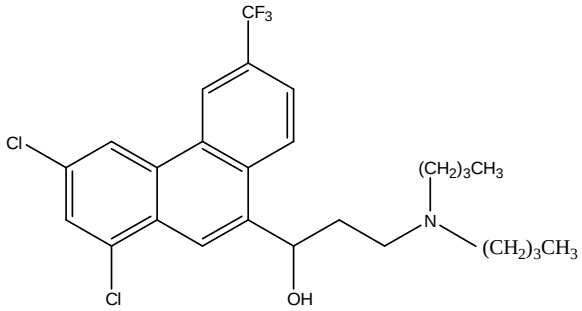
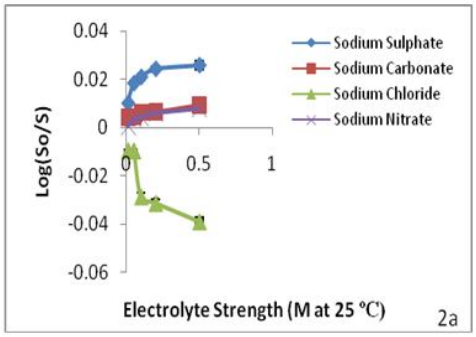


Figure 1. Chemical Structure of Halofantrine



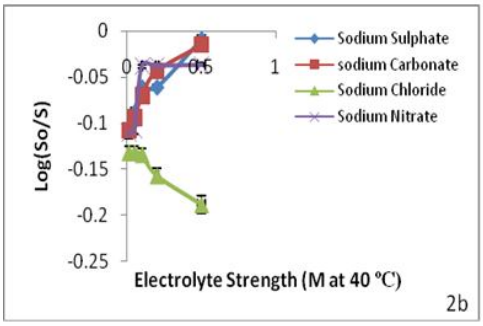


Table 1. Solubility of Halofantrine in Salt and Cosolvent Solutions at Different Temperature (10^{-3} M)

	25 °C [S_o= 3.028]					40 °C [S_o= 3.952]				
[Salt]	0.01	0.05	**0.10**	0.20	0.50	0.01	0.05	**0.10**	0.20	0.50
Na sulphate	2.958	2.902	2.885	2.863	2.853	3.864	3.705	3.488	3.485	3.094
Na carbonate	2.999	2.997	2.994	2.983	2.963	3.882	3.762	3.561	3.345	3.134
Na chloride	3.095	3.095	3.234	3.254	3.312	4.099	4.099	4.121	4.343	4.671
Na nitrate	3.024	3.003	2.998	2.985	2.972	3.908	3.873	3.306	3.301	3.294
% Cosolvent	**10**	20	40	80	100	**10**	20	40	80	100
PSB 80	3.215	3.219	3.310	3.345	3.451	4.100	4.103	4.215	4.498	4.834
P. glycol	3.002	2.897	2.873	2.845	2.834	3.686	3.487	3.365	3.215	3.129
Glycerol	2.967	2.911	2.904	2.809	2.801	3.810	3.498	3.453	3.156	3.115

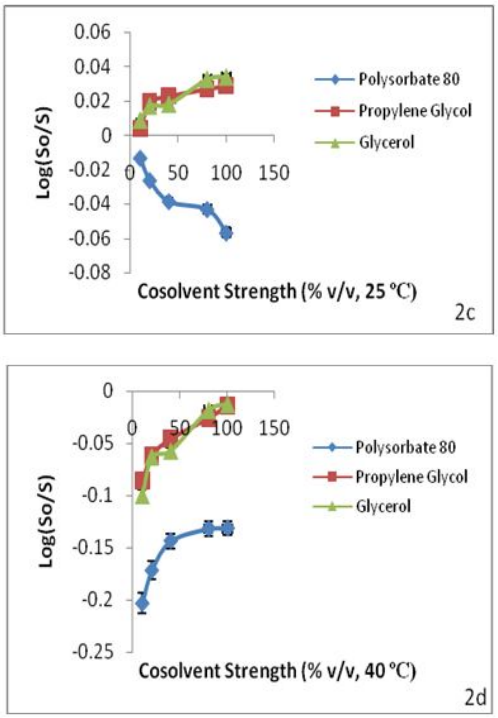


Figure 2. Log Linear Plot of Solubility of Halofantrine in (a) Electrolytes at 25 °C (b) Electrolytes at 40 °C (c) Cosolvents at 25 °C and (d) Cosolvents at 40 °C.

DISCUSSION

The dissolution of majority of solute is an endothermic process (positive ΔH^{o}_{trans}) according to Le Chatelier principles and such heat absorption results in collapse of crystal structure and promotes solubility (Chen and Shyu, 2001). As temperature increases, the absorption of heat by halofantrine lead to crystal structure collapse which could be responsible for over 20 percent increase in solubility of halofantrine for the 15 ºC rise in temperature. At all molar concentration of salts and temperature, Na_2SO_4, Na_2CO_3 and $NaNO_3$ did not improve the halofantrine solubility as much as NaCl; similarly polysorbate 80 and propylene glycol enhanced the solubility better than the glycerol. The results of thermodynamic of transfer shows that Na_2SO_4, Na_2CO_3, $NaNO_3$, propylene glycol and glycerol salted-out the drug over the concentration range studied while NaCl and polysorbate 80 salted-in halofantrine. The observed salt effect is the result of two factors: the charge-to-size ratio and structure breaking or structure making potential of the anions of the salt. The charge-to-size ratio is in the order $Cl^- < CO_3^{2-} < NO_3^- < SO_4^{2-}$ and salting out parameter is observed to decrease in that order. Na_2SO_4 salted-out halofantrine because SO_4^{2-} is a powerful structure maker (Sugunan and Benny, 1995) and reduces solubility of hydrophobic molecules by reducing proportion of available water molecules. The salting-in observed for Cl^- and polysorbate 80 could be attributed to their structure breaking potential which disperses repulsive forces between ions and neutral solute and solvent molecules; however, the structure breaking effect of polysorbate 80 appears to be much more sensitive to temperature (Figures 2c-d) due to observable salting out at higher temperature, though insignificant compared to other salts and co-solvents that salted-out halofantrine at every temperature (Figures 2a-b). The dissolution of a molecule in solvent is accompanied by enthalpy of solution, which may be endothermic or exothermic and decreases or increases the randomness of the dissolution. The decrease in solubility of halofantrine in SO_4^{2-}, CO_3^{2-}, NO_3^-, propylene glycol and glycerol as a result of the negative entropy change (Table 2) could be attributed to high hydrophobic hydration which leads to positive ΔG values, non-spontaneity of solubilization and a thermodynamically unfavourable medium for halofantrine solubilization. Similarly, the salting-in by Cl^- and polysorbate 80 is due to spontaneity and a higher thermodynamically favourable environment of solubilization.

Conclusion

The study shows that inorganic salts and co-solvents have varying effects on solubilization of halofantrine, a hydrophobic molecule. The parameters determined could be harnessed in further development of halofantrine for better solubilization, delivery, absorption and bioavailability. Vehicles that salted-out halofantrine could be used as external pseudo phase in matrix and structured drug delivery devices while those that salted-in the drug are better choice as internal pseudo phase to improve the loading efficiency and ensure entrapement within the matrices.

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