Effect of nanomeric structured micelles on metabolic kinetic study of two CNS drugs

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1. INTRODUCTION

Depression is estimated to affect nearly 340 million people worldwide and 18 million people in the US at any given time [1-2], making it the third most costly and disabling illness in the US [3-8]. By the year 2020, it is predicted that depressive illness will be the second leading cause of disability worldwide [9]. Duloxetine is a potent and balanced inhibitor of the reuptake of serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE). *In-vitro* and *in-vivo* it is used to treat depression, diabetic peripheral neuropathic pain and stress urinary incontinence [10-15]. Duloxetine is eliminated primarily in the urine after being extensively metabolized in the liver by oxidative enzymes, principally cytochrome P-450 (CYP) isoenzyme 2D6 and to a laser extent, CYPIAZ. Its elimination is primarily through hepatic metabolism, and biotransformation pathways involve oxidation of the napthyl ring, followed by conjugation and further oxidation. Major metabolities found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate.

Epilepsy is the most common serious neurological disorder, with an incidence of 50/100000 per year. A cumulative lifetime incidence of 1 in 20 and a prevalence of 1 in 200 [16]. Epilepsy is characterized by the periodic and unpredictable occurrence of seizures. It is the most prevalent neurological disorder, affecting 0.5% to 1% of the world wide population (45~100 million) [17-19]. Carbamazepine is an anti-convulsant drug which required approval for used as a AED in the us in 1974. It is also used as a treatment for patients with manic-depressive illness, post-herpetic neuralgia or phantom limb pain [20-24]. CBZ is extensively metabolized through several distinct biotransformation pathways. Quantitatively, the most important biotransformation is the epoxide-diol pathway of the azepine ring to form the chemically stable epoxide (CBZ 10, 11-epoxide), which has potent anticonvulsant activity n its even right [25]. CB epoxide has been identified in urine [26] and plasma [27] of man.

2. MATERIALS AND METHOD

The pseudo first order conditions were maintained in all reactions. The condition was maintained by using a large excess of drug over the oxidant i.e. [Drug] >> [V(V)]. The reaction was carried out in glass stoppard pyrex boiling tubes whose outer surface was coated black to eliminate photochemical effect. Reaction mixture containing approximate quantity of substrate solution and acid were taken in one flask. The oxidant solution was taken in other flak. The two flasks were placed in a thermostat (Toshniwall) of sensitivity ± 0.1ºC. When the two solutions attained the desired temperature of the water bath, they

3. RESULTS AND DISCUSSION

The oxidation reaction is third order reaction i.e. first order w.r.t. [V(V)], [DULT] and [CBZ], and [H^+] The reaction is found to be acid catalyzed below and above the cmc of anionic surfactant i.e. sodium lauryl sulphate.

When all the reactions are studied at the cmc of surfactant it shows acceleration of the reaction rate. The reaction shows that SLS and H^+ both favors the metabolic conversion of duloxetine and carbamazepine.

The drug obeyed the Beer's law over the range of 1.1µg/ml-4.2µg/ml and 0.035 mg/ml-0.36mg/ml for the both drug duloxetine as well as carbamazepine. The linear plot gave the regression equation and molar absorptivity and Sandell's sensitivity was also calculated (Table 1 and 2].

The activation parameters for the reaction in the aqueous as well as micellar media were calculated. Consistency in the calculated values of ΔG^* for these two oxidation reaction indicates that probably the same type of mechanism is operative for both reaction. The proposed mechanism is supported by the moderate values of energy of activation and other activation parameters. The fairly high values of ΔH^* and ΔG^* indicates that the transition state is highly solvated, while the negative ΔS^* suggests that the transition state is highly rigid with less degree of freedom in both drugs (Table 3 and 4).

The kinetic evidence shows that there is a complex formation between substrate and oxidant. As far as the oxidation of duloxetine is concerns, no mechanistic studies have been published. In this study activation parameters for the oxidation of duloxetine and carbamazepine by V(V) in both aqueous and micellar medium have been proposed and duloxetine and carbamazepine epoxide is identified as a oxidation product of duloxetine

The study compared the single and multiple dose pharmacokinetics of duloxetine and carbamazepine *in vitro* i.e. alone with V(V) and in presence of surfactant (SLS). The result shows that in the presence of SLS drug shows better metabolic oxidation as compared to when it was oxidized alone in aqueous media.

As it works on central nervous system (CNS), drug should be more available to the cells. To increase the bioavailability and solubility drug can be formulated with SLS.

Table 1 : Optical and Regression Characteristics of Duloxetine

Parameter	Result
λ_{max}	520 nm
Beer's Law Limit	1.1µg/ml – 4.2µg/ml
Molar Absorptivity (L mol^{-1}/cm)	5.3×10^6
Sandell's Sensitivity (µg cm^{-2}/ 0.001 Abs. Unit)	6.4×10^{-6}
Regression Equation (y= mx +c) Slope (m)	0.1495
Intercept (c)	0.0968
Correlation Coefficient (R^2)	0.9995

Table 2 : Optical and Regression Characteristics of Carbamazepine

Parameters	Result
λ_{max}	520nm
Beer's Law Limit	0.035 mg/ml – 0.36 mg/ml
Molar Absorptivity (L mol^{-1}/cm)	4.7×10^4
Sandell's Sensitivity (µg cm^{-2}/ 0.001 Abs. Unit)	4.9×10^{-4}
Regression Equation (y= mx +c) Slope (m)	2.0767
Intercept (c)	0.0038
Correlation Coefficient (R^2)	0.9983

Table 3 : Activation Parameters for the Metabolic Conversion of Duloxetine in Absence and Presence of SLS

Condition	Ea (kJ mol^{-1})	Δ H* (kJ mol^{-1})	Δ G* (kJ mol^{-1})	- Δ S* (JK^{-1} mol^{-1})
Aqueous	56.760	54.242	67.780	-44.71
Micellar	56.703	54.185	64.611	-34.39

Table 4 : Activation Parameters for the Metabolic Conversion of Carbamazepine in Absence and Presence of SLS

Conditions	Ea (kJ mol^{-1})	Δ H* (kJ mol^{-1})	Δ G* (kJ mol^{-1})	- Δ S* (JK^{-1} mol^{-1})
Aqueous	47.640	45.139	76.264	-99.264
Micellar	49.651	47.149	75.128	-83.921

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