ULTRASONICALLY-INDUCED BIREFRINGENCE OF DEXAMETHAZONE DISODIUM PHOSPHATE SOLUTIONS

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ABSTRACT

A detailed study of the ultrasonically induced birefringence has been performed in dexamethasone disodium phosphate (DEX-SP) solutions with propylene glycol by employing the Raman-Nath theory to evaluate the relative variations of the acoustic intensity. The birefringence in solutions was investigated as a function of frequency, ultrasonic intensity and concentration. Betamethasone, dexamethasone and their ester derivatives are synthetic glucocorticoids used as anti-inflammatory or immunosuppressive agents, and are used in treatment of allergies, arthritis, asthma, etc. The beta- and dexa- forms of these molecules are epimers with identical chemical structures except that the orientation of the methyl group at the C-16 position is in the opposite direction from the plane. Despite minor spatial differences in structures, different isomeric forms of an active pharmaceutical ingredient (API) may have vastly different physiological effects. One isomer can be beneficial, while the other isomer might be toxic to human beings.

Ultrasonically induced birefringence has been observed in various liquids and solutions[1]. For the small anisotropic molecules, the velocity gradient caused by ultrasound can directly induce the sinusoidal orientation. This causes the sinusoidal birefringence, which is proportional to the square root of the ultrasonic intensity $(W_u)^{1/2}$ [2]. For large anisotropic particles, the orientational motion cannot follow the sinusoidal velocity gradient. However, the radiation pressure, which is one of the typical quadratic acoustic effects, produces the stationary torque on the particle that induces the uniform and stationary orientation of the particles in the solutions[1,2]. In this case, the induced birefringence is proportional to the ultrasonic intensity W_u. The 'non-biased' detection technique was utilized for the ultrasonically induced birefringence measurements, which allows the detection of both the sinusoidal and stationary birefringence. If both the sinusoidal and stationary birefringence co-exists, the predominant birefringence will be observed. In this study, we performed concentration and temperature dependent measurements of ultrasonically induced birefringence. We obtained the intrinsic values of the stationary and transient birefringence for several dexamethasone disodium phosphate solutions and related those to the segmental anisotropy in polarizability. The results indicated that the induced birefringence is proportional to the ultrasonic intensity. We also measured the frequency dependence of the stationary birefringence to progress on the comprehensive understanding of the mechanism of the ultrasonically induced birefringence phenomenology in these glucocorticoid solutions.

INTRODUCTION

In a solution or a liquid, the medium is isotropic. If we apply an ultrasonic field of a specific frequency in this solution or liquid, this isotropic form is giving its place to an anisotropic form. The non-spherical molecules due to the presence of the ultrasound are forced to change their orientation and to align with the direction of the ultrasound propagation direction. This change causes a difference in density and thus in refractive index. This phenomenon is called ultrasonically induced birefringence. Birefringence may also be induced, not only by the

application of an ultrasound field, but also by an external magnetic or electric field [3]. The magnetically and electrically induced birefringence can be induced in chemical systems that exhibit magnetic or electrically properties, respectively. Unfortunately, the last two methods have limited application due to the influence of the required intense electric or magnetic field to the molecules [3,4,5].

The ultrasonically induced birefringence is a powerful tool in studying the dynamics of a given system. When we apply an ultrasound pulse into a liquid as we mentioned earlier the molecules starts to orient. This orientational move is not irrelevant but has a relation to the velocity gradient of the sound wave when we are referring to small particles. For very large particles and colloids fluids the birefringence is observed due to the ultrasonic torque which force the molecules to orient and align with its other [5,6]. Ultrasonically induced birefringence is used for the characterization of non-spherical and colloidal particles and the study of collective translational-rotational coupling motion of molecules which makes it very useful for characterizing glucocorticoids. When an ultrasound is propagating through a liquid changes the refraction index to the direction of the ultrasound propagation. This effect (birefringence) happens for the period where the ultrasound is on. When the ultrasonic field is off, the system returns to its initial isotropic state. The presence and the absence of the ultrasonic field lead to orientational phenomena (field on) and randomization phenomena (field off). From these experiments, one is able to extract information regarding the molecule size and shape from the value of the stationary birefringence (from electrically induced birefringence also the charge distribution and the presence of permanent or induced dipoles can be found). These types of phenomena can be seen by the difference of orientation and randomization time. Furthermore, from the Debye-Einstein equation the effective volume can be estimated [7].

For small anisotropic molecules the velocity gradient caused by the ultrasound can directly induce the sinusoidal birefringence, which is proportional to the square root of the ultrasonic intensity. For large anisotropic molecules the orientational motion cannot follow the sinusoidal velocity gradient. The ultrasound torque forces the particles to orient and finally leads to steady-state with a static birefringence. The stationary birefringence is proportional to the ultrasonic intensity [4,5,6].

In this study, we measured the ultrasonically induced birefringence in dexamethasone disodium phosphate diluted in propylene glycol. Dexamethasone phosphate also known as Decadron, Dexasone, Dodex and various others names is a corticosteroid medication. Corticosteroids are a class of steroid hormones which produced in the adrenal cortex of vertebrates or analogues of these hormones can be synthesized in a lab. Dexamethasone is a synthetic analogue and is classified as an anti-inflammatory medication. The molecule has two hydrogen bond donors and five hydrogen bond acceptors which make it candidate for aggregation. It is also soluble in water acetone, ethanol, chloroform, propylene glycol and some others organic solvents. Dexamethasone relieves inflammation in various parts of the body. It is used specifically to decrease swelling (edema), associated with tumors of the spine and brain, and to treat eye inflammation. We used ultrasonically induced birefringence in order to find out if the

dexamethasone can form hyper-molecular structures and acquire useful information regarding the molecular dynamics of the system.

EXPERIMENTAL

We prepared solutions of dexamethasone disodium phosphate in propylene glycol solvent and conducted experiments of ultrasonically induced birefringence in various temperatures and concentrations. We present here representative results for concentration 2mg DEX-SP/10ml propylene glycol solvent. For the birefringence measurements, a He-Ne laser has been utilized operating at 632.8nm. The power of the laser was set at 5mW. The laser-line passed through a temperature-controlled quartz cell with a fixed length of d=1cm. An electric high- voltage RF pulse was applied to a piezoelectric element that generated the ultrasonic pulse. This ultrasonic pulse was propagating through the cell in a vertical direction to the laser beam. In order to avoid heating and streaming effects a low-repetition rate of ultrasonic pulses were used. The duration of the pulses was adjusted to a certain value in order to achieve formation of standing wave inside the optical cell. This step is very important for accurate measurements of the ultrasonically induced birefringence. The non-biased detection technique was used to measure the sinusoidal and stationary birefringence.

RESULTS AND DISCUSSION

In order to evaluate the ultrasonic intensity at the specific element of the sample volume responsible for the ultrasonically induced birefringence, we measured the diffracted light from the density grating caused by the stationary ultrasonic wave in the liquid. This phenomenon is the so-called Debye-Shears effect. The speed of light is by far higher than the ultrasound velocity and thus, the variations in the refractive index constitute a stationary diffraction grating. The pulse length was set long enough to ensure that transient birefringence reaches its maximum (plateau). Information concerning the ultrasonic intensity can be obtained indirectly by measuring the light intensity emerging from the liquid. In fact, we sent the main maximum (0th-order) of the diffraction pattern into detector by means of an adjustable single slit. To add the necessary phase bias, a quarter-wave plate has been used.

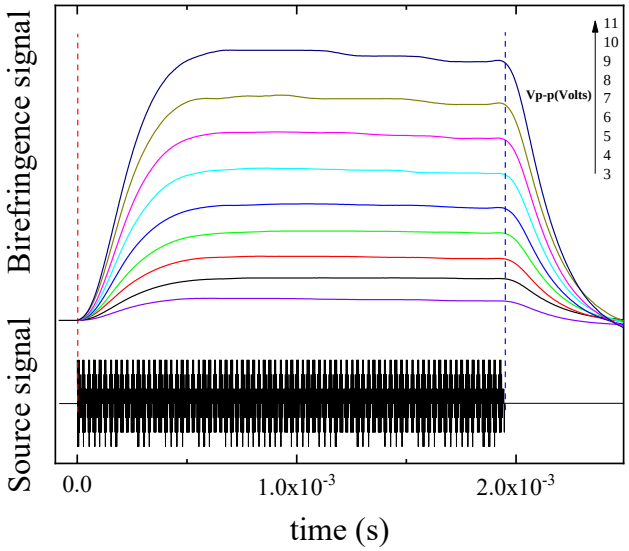

Figure 1. *Traces of transient ultrasonically induced birefringence of 2mg dexamethasone disodium phosphate dissolved in 10ml propylene glycol at 20°C for all applied voltage to the transducer. The frequency of the ultrasound waves applied to the liquid sample was 770 KHz. The applied ultrasonic pulse is also shown for comparison.*

In Fig. 1 are shown the applied ultrasonic pulse and the trace of the transient ultrasonically induced birefringence of DEX-SP solution as a function of the applied voltage corresponding to concentration 2mg DEX-SP/10ml solvent at 25°C. In the same graph is also shown the applied ultrasonic pulse. The observed rise and decay of the birefringence signal is assigned to orientation and disorientation relaxation. The different profiles of the orientation and disorientation relaxation times imply that the mechanisms that underlie in both processes are not the same.

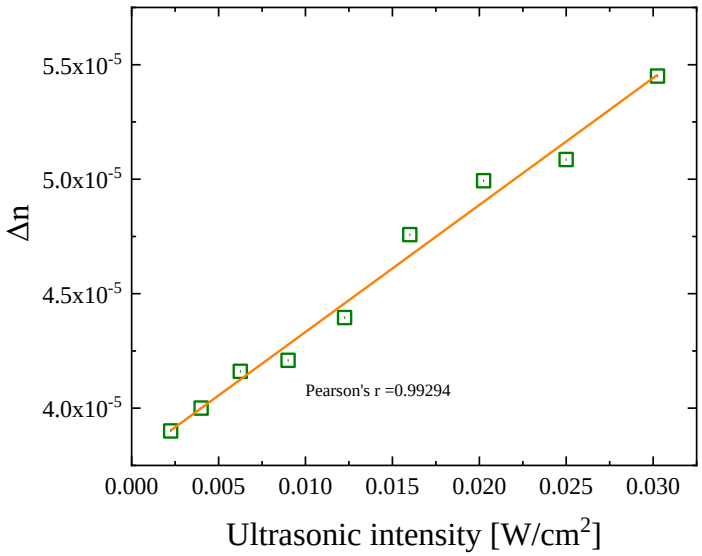

Figure 2. *Induced birefringence as a function of ultrasonic intensity of DEX-SP dissolved in propylene glycol at 20°C. The value of Pearson's R=0.99294 indicates an almost perfect linear dependency between birefringence and ultrasonic intensity. The frequency of the ultrasound waves applied to the liquid sample was 770 KHz.*

The ultrasonic intensity dependence of the induced birefringence is presented in Fig. 2. It seems that the birefringence is proportional to the ultrasonic intensity. Dexa-SP molecules have an equivalent radius much smaller than the ultrasonic wavelength and as a result tend to align the main axis of the non-spherical shape along the propagation direction of the ultrasonic beam.

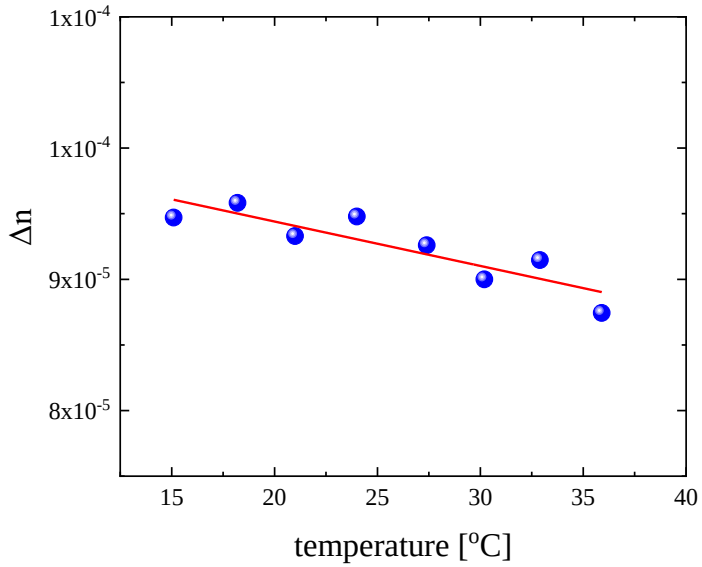

Figure 3. *Temperature dependence of the birefringence for Dexa-SP dissolved in propylene glycol at 20ºC. The results indicate a linear dependency between birefringence and temperature.*

In Fig. 3 we present the temperature dependence of the birefringence for Dexa-SP dissolved in propylene glycol at 20ºC. The results also in this case indicate a clear linear dependency between birefringence and temperature, although with decreasing trend.

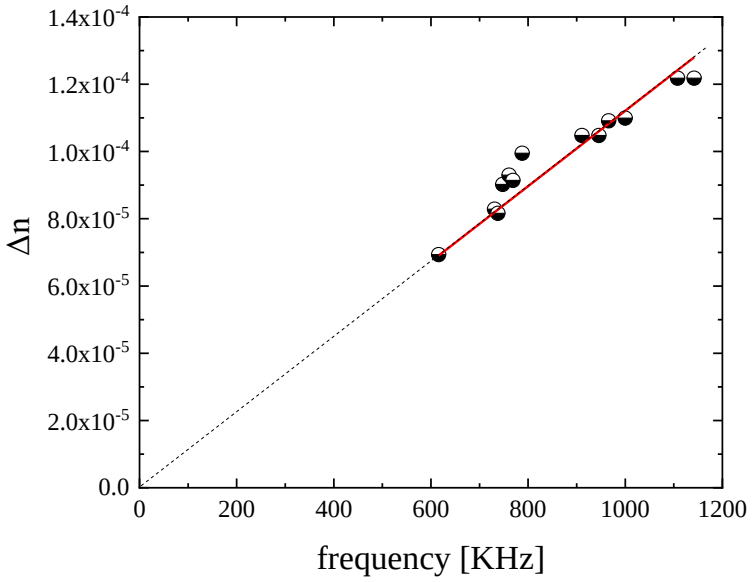

Figure 4. *Frequency dependence of the induced birefringence for Dexa-SP dissolved in propylene glycol at 20ºC. The results indicate a linear dependency between birefringence and ultrasound frequency.*

Fig. 4 illustrates the frequency dependence of the ultrasonically induced birefringence. The

results reveal that the birefringence is linearly dependent on frequency, which results from the translational velocity gradient between Dexa-SP and solvent molecules. With increasing the frequency of the ultrasound, the translational motion of Dexa-SP molecules impede relative to the solvent molecules. This translational velocity difference causes increase of the radiation pressure on the Dexa-SP molecules leading thus to birefringence increase with frequency. This experimental observation is expected if we consider that the ultrasonically induced birefringence is related to the mean orientation of the molecules, which is frequency dependent.

CONCLUSIONS

In this work we present a study of the ultrasonically induced birefringence in Dexa-SP molecules in solutions with propylene glycol. We employed Raman-Nath theory to evaluate the relative variations of the acoustic intensity. Birefringence signals are ascribed to the orientation of the molecules in the direction of the ultrasonic field applied. The static ultrasonically induced birefringence in solutions was measured as a function of ultrasonic intensity and found proportional to the ultrasonic intensity. The birefringence was linearly dependent on frequency, as resulted from the translational velocity gradient between Dexa-SP and solvent molecules. Concerning the transient behavior of the birefringence, we found that the rise and the decay times of the birefringence signal were not comparable implying discrete relaxation mechanisms.

ΒΙΒΛΙΟΓΡΑΦΙΑ

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