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Ultrasonic Studies on Lamivudine: β-Cyclodextrin and Polymer Inclusion Complexes

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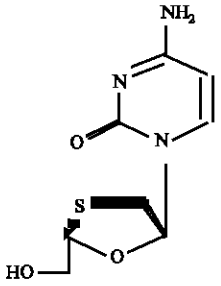
Abstract: The aim of the present study is to enhance the solubility and stability of drugs in addition of water-soluble polymer and carbohydrate complexes. The data show that the polymer polyvinyl alcohol (PVA) interacts with the free Lamivudine and with the Lamivudine; β-cyclodextrin (β-CD) inclusion complex, in both cases with particular intermolecular interaction was studied using ultrasonic technique under different concentrations at a temperature 303 K. Consequently, the reason of this study was to improve the biological performance of the drug through enhancing its solubility and stability. The binary and ternary mixtures prepared inclusion complexes of Lamivudine in β-CD and PVA. The presence of PVA, changes the drug: β-CD interaction, a Lamivudine: β-CD: PVA complex was formed. In addition, the presence of PVA produces a strong increase in the binding constant at a particular concentration (1.25%). In the ternary complex, the Lamivudine is wrapped at both ends for the β-CD. In this complex, the polymer seems to act as a bridge between both β-CD molecules that bind the Lamivudine.

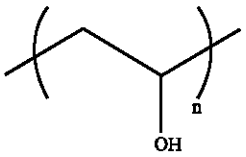
Key words: Lamivudine, β-cyclodextrin, polyvinyl alcohol, inclusion complexation

INTRODUCTION

Inclusion complexation with β-cyclodextrins (β-CD) has been widely exploited to improve solubility and stability, of various drug molecules (Uekama *et al*., 1998). Lamivudine (L-2', 3'-Dideoxy-3'-thiacytidine) (Scheme 1) is a potent reverse transcriptase inhibitor of the class of Nucleoside Analogue Reverse Transcriptase Inhibitors (NARTI) (Sweetman, 2002). It has been used for the treatment of human immunodeficiency virus type 1 (HIV-1), which causes the acquired immunodeficiency syndrome (AIDS) (Siegfried *et al*., 2006) and of chronic (Manas Garcia *et al*., 2005) and acute (Torii *et al*., 2002) hepatitis B (HBV). However, the efficiency of complexation is often not very high and therefore, relatively large amounts of β-CD must be used to obtain the desired effect (Loftsson and Brewster, 1996). On the other hand, for a series of reasons including cost, production capacity, possible toxicity, problems of formulation bulk, etc., pharmaceutical dosage forms should contain as small amounts of β-CD as possible (Kagathara *et al*., 2000). When polyvinyl alcohol (PVA) (Scheme 2) was added, all the data clearly show that the effect of the polymer on the complexing ability of β-CD (Scheme 3) depends on the nature of the β-CD and the polymer interactions between both of them. The nature and the interactions of the components in the ternary complex, also change the chemical behavior of the drug. The addition of a third component such as water-soluble polymers enhances the efficiency of drug-cyclodextrine complexation. This solubilization enhancement is synergistic (Loftsson *et al*., 1994; Ganzerli *et al*., 1996).



Scheme 1: The chemical structure of Lamivudine



Scheme 2: The chemical structure of polyvinyl alcohol (PVA)

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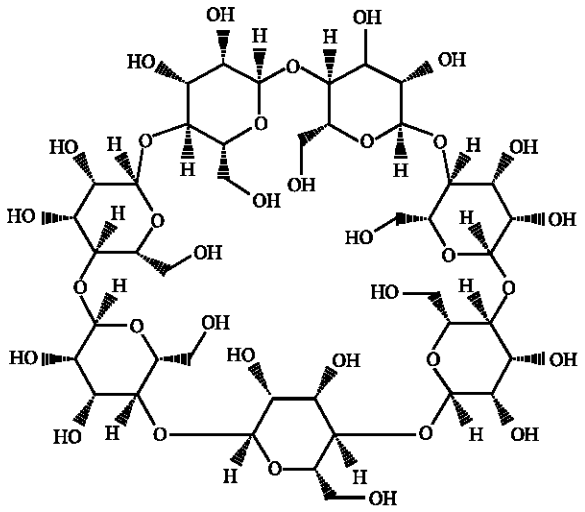

Scheme 3: The chemical structure of β-cyclodextrin (β-CD)

MATERIALS AND METHODS

Materials: Lamivudine (Sigma, USA) a sparingly soluble drug with the formula $C_8H_{11}N_3O_3S$, molecular weight (229.26 g mol^{-1}) Polyvinyl alcohol was obtained from (Fluka AG Switzerland) with the formula-$_{OH}(-CH_2-CH-)_n$-M.W 125000 g mol^{-1}. β-cyclodextrin (β-CD) (M.W 1135.01 g mol^{-1}) was purchased from (E. Merck, Germany) stated by the manufacturers. These reagents were considered sufficiently well characterized by the manufacturer to be used without further purification. Conductivity water was used for the preparation of all aqueous solutions.

Methods: Initially, three concentrated aqueous solutions were prepared: (1) Lamivudine/H_2O: prepared as described above. (2) Lamivudine/PVA/H_2O: prepared by weighing the required amount of PVA, using the aqueous drug solution (1) as solvent. (3) Lamivudine/β-CD/PVA/H_2O: prepared by weighing the required amount of β-CD, using the aqueous drug/polymer solution (2) as solvent. Solutions with variable PVA concentrations were obtained by successive dilution of (2) with (1). Solutions with variable β-CD concentrations and constant PVA content were obtained by successive dilution of (3) with (2). All measurements were carried out at room temperature of 303 K.

Ultrasonic measurements: The ultrasonic velocity, density and viscosity of these solutions were measured. Ultrasonic velocity was measured using single-crystal continuous wave interferometer (Mittal Enterprises, New Delhi) operating at 3 MHz with an accuracy of ±0.05%. The densities were measured using specific gravity bottle and viscosity is measured using Ostwald's viscometer to an accuracy of ±0.2 parts in 10^4 and ±0.2%, respectively.

Using the measured date, the acoustical parameters such as adiabatic compressibility (β) and internal pressure (π_i), have been calculated using the following standard expressions given in our previous paper (Ramesh *et al.*, 2006).

- Adiabatic compressibility

$$\beta = \frac{1}{U^2\rho}$$

- Intermolecular free length $L_f = k\beta_s^{1/2}$
- Internal pressure

$$\pi_i = bRT\left[\frac{k\eta}{U}\right]^{1/2}\frac{\rho^{3/3}}{M^{7/6}}$$

[K-Boltzman constant, b-Cubic packing factor, R-Gas constant, T-Absolute temperature, M-Effective molecular weight]

- Solvation number

$$Sn = \frac{M_2}{M_1}\left[1 - \frac{\beta}{\beta_0}\right]\left[\frac{100 - x}{x}\right]$$

RESULTS AND DISCUSSION

Ultrasonic analysis: Using the measured values of ultrasonic velocity, density and viscosity of the solutions, other acoustical parameters viz., adiabatic compressibility, intermolecular free length, internal pressure and solvation number are calculated and are shown in Table 1 and 2. Ultrasonic velocity increases with increase in concentration of drug, carbohydrate and polymer in water. Density and viscosity increases with the concentration in carbohydrate and polymer in aqueous solutions. Adiabatic compressibility (β) and intermolecular free length (L_f) decreases with increase in concentration of drug, carbohydrate and polymer mixture. Internal pressure (π_i) decreases with increase in concentration of polymer. Solvation number decreases with increase in concentration of drug, carbohydrate and polymer.

In all the three systems studied, the velocity is gradually increasing with concentration at room temperature shown in the Table 1 and 2. The variation in velocity is much higher in the β-cyclodextrin-water system and PVA-water it is due to the formation of intermolecular hydrogen bonding between the molecules. This behaviour may be explained as follows: the molecules of drug and polymer/carbohydrate (Table 2) are randomly coiled in solution and the chains have no overall tendency to adapt to any particular conformation (Geetha and Rakkappan, 2003). Dissolved macromolecules

Table 1: Ultrasonic velocity and related acoustical parameters in the aqueous solution of lamivudine, polyvinyl alcohol, β-cyclodextrine at 303 K

Samples	Conc. (%)	U (m sec^{-1})	ρ (kg m^{-3})	η (×10^3 Ns m^{-2})	β (×10^{10} N^{-1} m^2)	L_f (Å)	π_i (×10^{-6} pascal)	S_n
Lamivudine	0.0	1502	995	0.7970	4.4548	0.4211	25.855	-
	0.5	1522	1005	0.8158	4.2954	0.4135	475.802	30.6770
	1.0	1526	1007	0.8807	4.2644	0.4120	325.672	26.0680
	1.5	1531	1008	0.9014	4.2324	0.4104	268.086	24.0830
	2.0	1537	1010	0.9539	4.1911	0.4084	243.494	23.6950
	2.5	1543	1011	0.9951	4.1544	0.4066	228.517	23.0710
	3.0	1548	1013	1.0134	4.1195	0.4049	217.105	22.4810
PVA	0.0	1502	995	0.7970	4.4548	0.4211	25.855	-
	0.5	1534	1017	1.5393	4.1785	0.4078	446.284	72.7740
	1.0	1537	1022	1.6196	4.1419	0.4060	226.420	75.2850
	1.5	1540	1027	1.7300	4.1057	0.4042	151.617	81.1130
	2.0	1547	1029	2.1149	4.0607	0.4020	122.050	89.7540
	2.5	1550	1031	2.6653	4.0371	0.4009	106.921	93.7300
	3.0	1561	1034	2.7426	3.9689	0.3975	88.272	107.8910
β-CD	0.0	1502	995	0.7970	4.4548	0.4211	25.855	-
	0.5	1454	998	0.8772	4.7395	0.4343	373.226	-71.9920
	1.0	1469	999	0.8948	4.6386	0.4297	200.987	-39.8450
	1.5	1483	1003	0.9011	4.5333	0.4248	140.440	-15.8920
	2.0	1492	1005	0.9075	4.4698	0.4218	110.147	-3.4907
	2.5	1524	1007	0.9514	4.2756	0.4125	93.241	28.4510
	3.0	1546	1008	0.9677	4.1506	0.4065	81.159	45.6820

Table 2: Ultrasonic velocity and related acoustical parameters in the aqueous solution of lamivudine (1 %) + polyvinyl alcohol, β-cyclodextrine (1 %) + polyvinyl alcohol, β-cyclodextrine (1 %) + polyvinyl alcohol (1%) + lamivudine at 303 K

Samples	Conc. (%)	U (m sec^{-1})	ρ (kg m^{-3})	η (×10^3 Ns m^{-2})	β (×10^{10} N^{-1} m^2)	L_f (Å)	π_i (×10^{-6} pascal)	S_n
Lamivudine (1%)	0.00	1526	1007	0.8807	4.2644	0.4120	325.672	26.068
+polyvinyl alcohol	0.25	1536	1021	1.5568	4.1513	0.4065	343.085	79.959
	0.50	1539	1024	1.5916	4.1230	0.4051	284.872	59.079
	0.75	1541	1028	1.6387	4.0963	0.4038	244.554	53.997
	1.00	1544	1030	1.6781	4.0725	0.4026	213.578	52.347
	1.25	1548	1033	1.7264	4.0397	0.4010	190.157	54.723
	1.50	1555	1035	1.8143	3.9957	0.3988	173.125	60.178
	1.75	1562	1038	1.9081	3.9485	0.3964	159.498	66.288
	2.00	1574	1046	2.2126	3.8588	0.3919	155.943	80.790
β-cyclodextrine (1%)	0.00	1469	999	0.8948	4.6386	0.4297	200.987	-39.845
+polyvinyl alcohol	0.25	1512	1009	1.3425	4.3351	0.4154	192.432	304.036
	0.50	1517	1013	1.4210	4.2896	0.4132	162.600	206.623
	0.75	1522	1020	1.5728	4.2322	0.4104	144.890	184.938
	1.00	1528	1026	1.6234	4.1745	0.4076	127.261	179.306
	1.25	1535	1031	1.7782	4.1164	0.4048	116.966	180.088
	1.50	1538	1037	1.9143	4.0767	0.4028	108.209	178.177
	1.75	1544	1044	2.0498	4.0179	0.3999	100.892	184.383
	2.00	1549	1048	2.1327	3.9768	0.3979	93.417	186.584
β-cyclodextrine (1%)	0.00	1528	1026	1.6234	4.1745	0.4076	127.261	179.306
+polyvinyl alcohol+	0.25	1535	1036	1.6428	4.0966	0.4038	135.302	129.008
lamivudine	0.50	1539	1043	1.6741	4.0479	0.4014	142.575	100.999
	0.75	1544	1051	1.6928	3.9911	0.3986	148.513	94.695
	1.00	1551	1065	1.7185	3.9032	0.3942	154.587	102.517
	1.25	1580	1080	2.4379	3.7090	0.3842	188.166	137.795
	1.50	1572	1081	1.7658	3.7434	0.3860	163.622	104.423
	1.75	1586	1096	1.7924	3.6273	0.3800	168.260	111.811
	2.00	1598	1108	1.8279	3.5343	0.3751	172.853	112.839

frequently find molecular association complexes either with species of low molecular weight solvent with other macromolecules. The Lamivudine-water, PVA-water and β-CD-water interaction due to hydrogen bonding is a major source of ultrasonic relaxation. The mechanism should produce the increase in density and ultrasonic velocity with increase in concentration (Sundaresan and Srinivasa Rao, 1994; Geetha and Rakkappan, 2005a). These measurements suggested the formation of a more rigid structure as a function of concentration, possibly due to bonding of polymer and carbohydrate molecules to water at its carboxyl sites (Jin *et al*., 1995).

In the hydrogen bonded systems, the intermolecular free length, internal pressure decreases with increase of hydrogen bond strength. The decrease in the value of adiabatic compressibility and inter-molecular free length with increase in concentration at room temperature further supports the interaction between the solute and solvent. Density and viscosity increases with the concentration in drug, carbohydrate and polymer in aqueous solutions.

The positive value of S_n indicates the structure-forming tendency of the carbohydrate and polymer. The resultant value of the S_n depends upon solvent-solute and solute-solute interactions occurring in the solution (Kagathara *et al*., 2000; Geetha and Rakkappan, 2005b). Increase in S_n with concentration indicates predominant solvent-polymer interaction. Thus, dipole-dipole interaction of the opposite type profoundly favours the solvating tendency.

The above, mentioned results reveal that the ternary system Lamivudine-β-CD-PVA improves significantly the therapeutic efficacy of the drug at 1.25% concentration.

CONCLUSIONS

In conclusion, the molecular association of water-soluble polymers to Lamivudine/β-CD systems would offer a promising drug delivery system having the great advantage of reducing the dose of the drug. PVA interacts with free Lamivudine and with the lamivudine: β-CD inclusion complex. The experimental data show that a Lamivudine: β-CD complex is formed at all the PVA percentages studied. This result shows that the guest and not only the β-CD; polymer interaction, plays an important role in the formation of the ternary complex.

The molecular interaction for Drug: β-CD molecules increase as the PVA concentration increases at 1.25% PVA. In the ternary complex, Lamivudine is wrapped at both ends by the β-CD. The data suggest that the polymer acts as a bridge between both β-CD molecules that bind the Lamivudine.

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