Adsorption of Racemic Compound on Chiral Polymer: Enantioselectivity Prediction and Interpretation from Molecular Orbital Theory

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***Abstract*-Adsorptive interaction of racemic compound with chiral polymers has been analysed from a study on the adsorption in liquid phase. Adsorption affinity which is expressed as the slope of the linear region of the isotherm for S and R isomer of the racemic compound is found to be different for different chiral polymers used as adsorbent systems. The adsorptive interaction computed from frontier orbital theory seems to correlate well with the experimentally measured adsorption affinity of different isomers. Electronic states of adsorbent and adsorbate were calculated by the semiempirical molecular orbital (MO) method exploiting HOMO/LUMO interaction using PM5 wave function through a geometric optimization method. The experimentally measured adsorption affinity, enthalpy of adsorption for different isomers and selectivity seems to correlate well with the adsorptive interaction energy computed from molecular orbital theory. The result of the investigation provides an implication to design suitable chiral polymer for resolution of racemic compounds.**

Keywords- Chiral Polymer; Adsorption Affinity; HOMO; LUMO; Interaction Energy

I. INTRODUCTION

The racemic resolution or chiral separation of one enantiomer from others is in demand for the production of pharmaceutically important compound as many pharmaceuticals exist on stereoisomers, with each isomer having different activity. The appropriate separation techniques for large scale resolution of chiral molecules are a challenging research where chiral separation of racemic mixtures of pharmaceuticals through chiral polymeric membranes represents a promising system for future commercial application. In this regard, we have been studying membrane and adsorptive separation processes for resolution of some pharmaceutically important compounds [1-4].

Chiral polymeric membranes are able to resolve optical isomers due to chiral properties such as chiral recognition sites. This type of membranes act as selective barriers in the resolution process, and they selectively transport one enantiomer due to the stereospecific interaction between the enantiomer and chiral recognition sites, thereby producing a permeate solution enriched with one enantiomer. The different binding affinities of two enantimers may be the result of different hydrogen bonding, hydrophobic, coulombic, Vander Waals interactions and steric effects with the chiral polymers [5]. In the resolution of racemic compounds by enantioselective membrane, one enantiomer preferentially adsorbs to the chiral recognition sites in the enantioselective membranes near the feed phase due to a higher binding affinity. It is thereafter, continuously adsorbed and desorbs from chiral site to the next, and at last it is transported toward the stripping phase. The other enantiomer, which has no or less specific binding affinity for the chiral environment, passes through the membrane by diffusion [5]. Thus for studying permeation of enantiomer through enantioselective membrane, it is also important to study the adsorption kinetics of the membrane. For separation and purification of some racemic compounds with therapeutically importance we have been studying membrane and adsorptive separation processes [1, 2]. Due to high concentrating factor, adsorption can satisfy the requirements of high recoveries and large volume reduction, and an efficient separation method. If adsorption is used for large scale separation, binding selectivity is considered to be an important factor. By characterizing the effect of surface chemistry on the energetic of adsorption, it is possible to design sorbents, which can selectively absorb solutes through enhanced binding energies.

For adsorption of racemic compound enantioselective membranes have nowadays been prepared and adsorption studies made [3]. Despite the success in producing this type of chiral membrane with well-defined physical properties, there are no studies of molecular details of the adsorption process. Due to the limited understanding of the solute – solvent binding interaction, adsorption operations have been developed empirically, and this empirical knowledge is insufficient to address such practical issues as improving binding strengths to facilitate on–off chromatographic operation, enhancing binding selectivities to permit separation of desired product from other chemically similar compounds, and reducing nonspecific adsorption (i.e. fouling). Adsorptive interaction and adsorption affinity are the fundamental aspects of study for assessing the feasibility of an adsorption process for

practical application. As regard, analytical as well as preparative scale separation of racemic compounds by membrane chromatography is yet to be established well.

Adsorption properties of aromatic adsorbent group of aromatic compounds influence adsorption and desorption characteristics of the adsorbate in liquid phase [6]. Thus the electronic state of adsorbent, adsorbate and solvent is very important to interpret adsorptive interaction in the liquid phases. A molecular orbital (MO) calculation is considered to be a powerful tool to study the adsorptive interaction based on charge transfer. For complex adsorbent surface, a three-body interaction occurs among adsorbent, adsorbate and solvent and so it is difficult to execute the MO calculation for the liquid phase adsorption directly. An adsorption model is necessary to overcome the difficulty in the MO calculation.

The Frontier orbital theory is a famous theory giving a reactivity index which is considered to be useful to study the charge transfer interaction. According to this theory, the adsorptive interaction is given by the mixing of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). Hence, the purpose of the present work is to propose an estimation procedure of adsorptive interaction in the liquid phase using the Frontier Orbital Theory.

For a specific application, the understanding of the sorption phenomena plays a crucial role in the selection of appropriate adsorbent. Adsorptive interaction and adsorption affinity are the fundamental aspects of study for assessing the feasibility of an adsorption process for practical application.

Usual experimental protocol to quantify these is to determine the adsorption equilibria and enthalpy of adsorption. However, theoretical interpretation is highly essential for surface modification and molecular design of adsorbents with high selectivity and capacity at the same time, providing favorable adsorption isotherms. Molecular modeling and simulation along with experimental investigation is expected to provide a thorough understanding of the microscopic and macroscopic properties of solute molecules in porous membrane. In this paper, we have reported experimental results on adsorption isotherm and enthalpy of different isomers of racemic drug compounds of pharmaceutical importance with polymeric membrane prepared from chiral polymers and theoretical estimate of interaction energy. Such an exercise is thought to be highly useful for design of better enantioselective adsorbents for process application. The theoretical treatment of molecular interaction is based on frontier orbital theory. It has been developed to describe several molecular phenomenon involving molecular interactions by calculating interaction energies for the corresponding geometric structures of the interacting molecules with several case studies [7-11] reported in the literature.

II. MATERIALS AND METHODS

A. *Materials*

Lipase, Atenolol, Captopril, Salbutamol, Propranolol hydrochloride, Trans sobrerol and polysulfone (average mol. Wt. 30,000) were supplied by Aldrich Chemical Company, USA, N-methyl pyrrolidone (NMP) was supplied by SRL-India. All reagents are 99% pure and used as such. The chiral polymers were prepared by the method reported in our earlier publication [2] wherein characterization of same has been discussed. The values of thermodynamic parameters calculated by SCIGRESS software for chiral polymers and drug molecules are shown in Table 1.

TABLE 1 VALUES OF THERMODYNAMIC PARAMETERS FOR CHIRAL POLYMERS AND RACEMIC COMPOUND

Compound	Heat of formation (kJ mol^{-1})	Enthalpy (kJ mol^{-1})	Heat capacity (kJ $mol^{-1}K^{-1}$)	Entropy (kJ $mol^{-1}K^{-1}$)	Free energy (kJ mol^{-1})
Chiral polymer 1	-310.489	142.03	0.765	1.424	-101.564
Chiral polymer 2	-487.228	176.54	0.986	1.659	-224.294
Chiral polymer 3	-415.253	196.97	1.084	1.838	-145.708
Trans sobrerol	-108.772	33.39	0.204	0.431	-46.674
Captopri	-126.873	49.78	0.284	0.585	-46.402
Salbutamol	-150.747	44.33	0.246	0.546	-85.169
Atenolo	-126.48	58.49	0.336	0.676	-30.857
Propranolol Hydrochlorid	-81.604	57.82	0.323	0.688	-1.993

B. Adsorption Isotherm

Equilibrium isotherms were obtained by contacting 20 ml of aqueous solution of racemic compound with different amount of chiral polymer in a thermo stated shaker maintained at 25 ± 0.5^{o}C for 4 hours. Preliminary runs showed that the adsorption equilibrium was achieved after 4 hours of contact time for all tested polymer. The initial concentration of the racemic compound

was taken between 5 and 10 mM. After attainment of equilibrium, the solution was analyzed by HPLC chiral column. The amount of isomer per gram of adsorbent q (mol/g) was calculated as $q = V\Delta C/ W$, where V is the solution volume (L) and W is the weight of the adsorbent (g).

Adsorption rate experiments were conducted in the liquid volume 20 ml with 0.05-0.2 g of adsorbents. The concentration of isomer in the liquid phase was monitored by HPLC analysis at equal interval of time till the equilibrium is attained.

The HPLC measurements were carried out on a Waters modular system consisting of two 510 pumps, an automated gradient controller, U6K injector and a 486 tunable absorbance detector. The chiral column required for resolution of racemic compound with eluents is reported in our earlier publication [3]. All chiral columns were purchased from DAICEL CHEMICAL INDUSTRIES Ltd.

C. Measurement of Enthalpies Using Van't Hoff Plots

Van't Hoff method was used to estimate the enthalpy of adsorption by relating the temperature dependence of the adsorption equilibrium constant. The Van't Hoff method utilizes two thermodynamic relationships, the first being

$$\Delta G^o = - RT \ln K = - RT \ln (\Psi q / C_e) \quad (1)$$

where, ΔG^o is the standard free energy change of adsorption, R is the universal gas constant, T is the absolute temperature in degree Kelvin and K is the equilibrium constant for the adsorption process. At low solute concentration adsorption is limited to the linear region of the isotherm and hence the equilibrium constant can be related to the adsorption affinity (q/C_e). The factor Ψ includes the terms for activity coefficient of the solute in the two phases and activity of the unbound adsorption sites. For a narrow range of solute concentrations, Ψ is assumed to be constant under the standard conditions.

The second thermodynamic relationship used in the Van't Hoff method is

$$\Delta G^o = \Delta H^o - T\Delta S^o \quad (2)$$

where, ΔH^o is the standard enthalpy change and ΔS^o is the standard entropy change of adsorption. Combining the two equations, the following equation is obtained.

$$\ln (q / C_e) = - \Delta H^o / RT + (\Delta S^o / R - \ln \Psi) \quad (3)$$

Thus, a plot of ln (q/Ce) versus 1/T gives a straight line with a slope of $- \Delta H^o / R$, from which $- \Delta H^o$ can be calculated under the assumption that ΔH^o, $- \Delta S^o$ and Ψ are constant over the temperature range of study.

D. Adsorptive Interaction in Aqueous Solution:

1) Molecular Orbital (FO) Calculation

Molecular orbital provides information on the basis of electronic states of adsorbents in an adsorption system, which will exploit to sorbent–solute interactions. In order to calculate electronic states of adsorbents by MO (molecular orbital) method, it is necessary to provide a structural (molecular) model of the adsorbents as discussed by previous workers and we have extended successfully the model for calculation of β-lactum antibiotics and some other biomolecules on polymeric resins [12, 13]. Recently, the MO theory has been exploited to correlate Freundlich isotherm parameter for adsorption of phenol derivatives [14]. Mardis et al. [15] have calculated standard free energy of binding using quantum mechanical calculations to elucidate the mechanism of selectivity of oxygenated aromatic compounds onto acrylic ester sorbent XAD-7. We use a chiral polyamide (Fig. 1) as the cluster models for the surface model of chiral polymers as shown in Fig. 2(a), Fig. 2(b) and Fig. 2(c). Tamon et al. [9] have used cluster models to study the adsorptive interaction of organic compounds on activated carbon and synthetic adsorbents. The cluster size is very important in the MO calculation. If the cluster size is small, the size seriously influences the electronic state of adsorbent surface. So, we have calculated the electronic state of the cluster models adopting the minimum cluster size to get the more appreciable influence on the energy level. In the MO calculation, the structure of chiral polymers and racemic compounds were determined by a geometry optimization method using standard procedure as shown in Fig. 2 and Fig. 3. The geometry of the molecule was found by minimizing their total energies with respect to the corresponding geometric variables i.e. bond length, bond angles and dihedral angles.

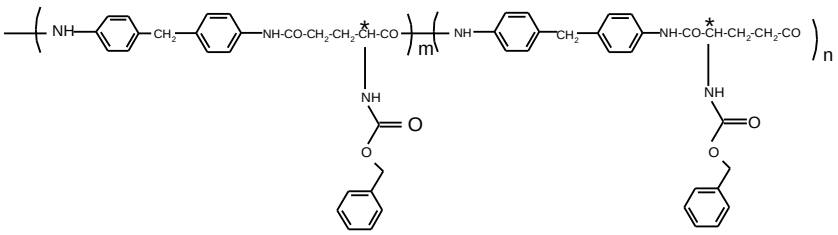
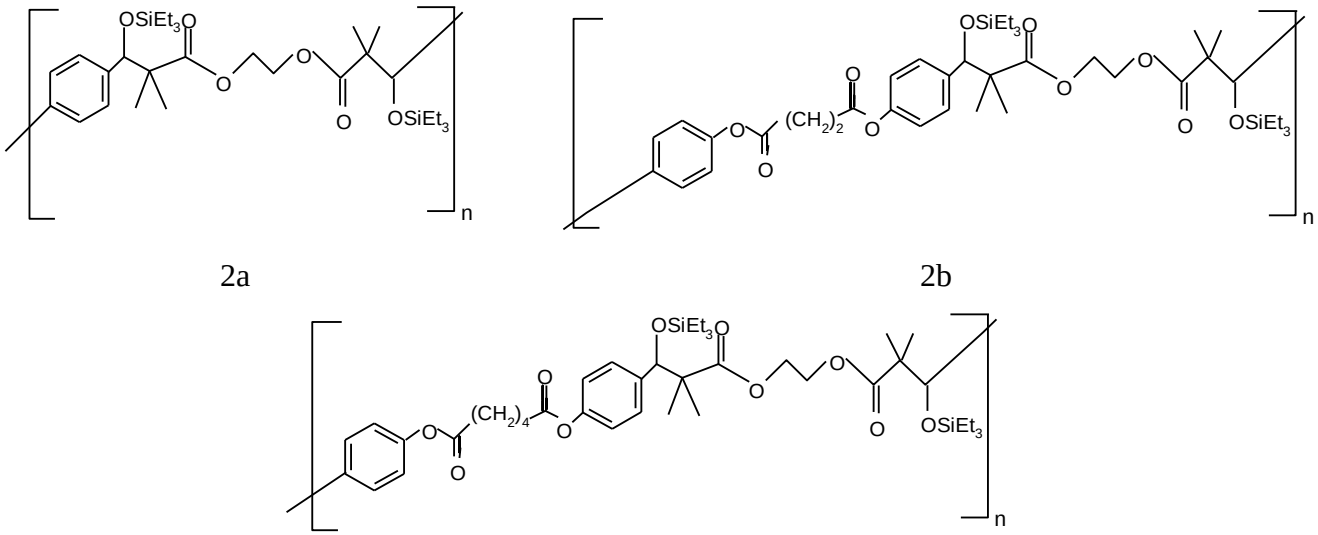


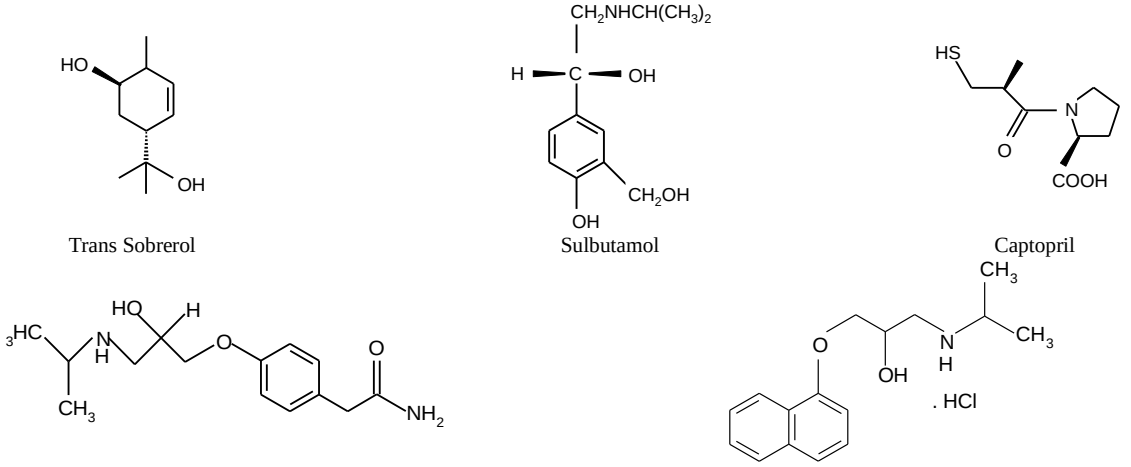
Fig. 1 Structure of chiral Polyamide



2a 2b

2c

Fig. 2 Structure of chiral polymer



Trans Sobrerol Sulbutamol Captopril

Atenolol Propranolol hydrochloride

Fig. 3 Structure of racemic compounds

The electronic state of adsorbents and adsorbates can be determined by semiempirical molecular orbital calculations. Though several semiempirical MO methods such as Austin model (AM1), complete neglect of differential overlap (CNDO), modified intermediate neglect of differential overlap (MINDO), modified neglect of differential overlap (MNDO), parameterized model number 3 (PM3), and parameterized model number 5 (PM5) can be used for calculation of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies, the basis of which may be understood from the solute–

solvent model (Fig. 4). However, in our case we have used PM5 as it gives satisfactory results because all the parameters for most of the atoms are available in PM5. All these methods are semiempirical and used for the quantum calculation of molecular electronic structure in computational chemistry and based on the neglect of differential diatomic overlap integral approximation.

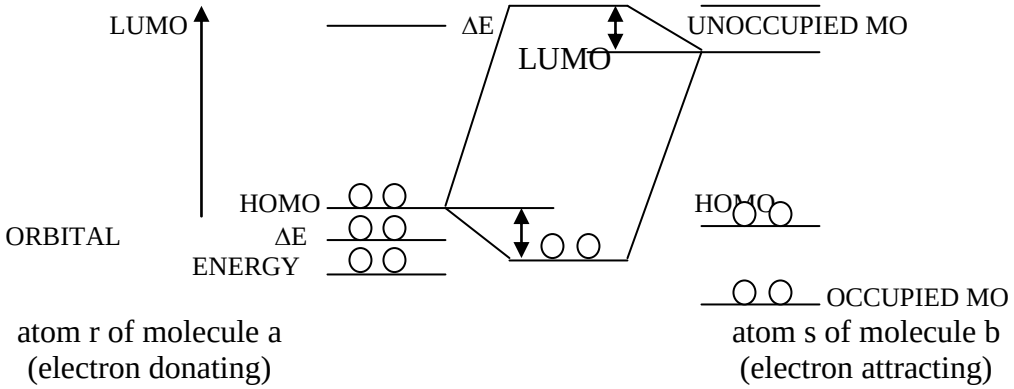


Fig. 4 Conceptual diagram of orbital mixing

2) Frontier Orbital (FO) Theory

The interaction energy between adsorbate and adsorbent is calculated on the basis of the frontier orbital theory (FOT) proposed by Fukui et al. [10]. According to FOT, two body interactions such as adsorbent–adsorbate, adsorbent–solvent, are regarded as the mixing of HOMO and LUMO. The HOMO energy is a measure of how hard it is to remove an electron from a neutral molecule and the LUMO energy is a measure of how hard it is to add an electron to the neutral molecule. Fig. 4 shows the concept of MO mixing. In this figure, molecule 'a' is electron donating, and molecule 'b' is electron attracting. Considering the charge transfer from atom r of molecule A to atoms of molecule B the energy level of HOMO of molecule 'a' changes to the more stable level by orbital mixing. On the other hand, the energy level of LUMO of molecule 'b' attains a more unstable level. The energy difference ΔE shown in Fig. 4 is called perturbation energy. The second order perturbation expression for the energy that accompanies the interaction can be derived, and the perturbation energy ΔE caused by the HOMO–LUMO interaction is calculated by Tamon et al. [9] which is given by Eq. (4)

$$\Delta E = \frac{2(C_r^* C_s^* \Delta\beta)^2}{|E_a^* - E_b^*|} \tag{4}$$

where E_a^* and C_r^* are the HOMO energy and orbital coefficient of the atom "r" of electron attracting molecule "a", respectively. $E_b^*$and C_s^* are the LUMO energy and the orbital coefficient of atom "s" of electron donating molecule "b". For MO calculation of adsorbent and adsorbate molecules we used Quantum CAChe software. The optimized geometry of the racemic compounds and cluster model of adsorbents can be found by minimizing their total energies with respect to the corresponding geometric variables i.e. bond length, bond angles and dihedral angles. Then the optimized structures were run in the PM5 Hamiltonian for semiempirical calculations. The output of the computer aided programme gives the HOMO–LUMO energies and their respective orbital coefficients of the required atoms. The square of the coefficient indicates the existence probability of an electron, and the 1S orbital for H atom, $2P_x$, $2P_y$ and $2P_z$ orbitals for C, O, N and S were taken into account to estimate ΔE. Δβ is the inter orbital interaction integral between the interacting orbitals of atoms, which is proportional to the overlap integral. Once the frontier orbital model is assumed, the choice of distance separating the interacting orbitals is important as the value of Δβ depends on the distance. We have chosen a distance of 0.242 nm because only at a distance of 0.25 nm, the positive lobe of one orbital starts overlapping the negative of the other and vice versa [16]. The following values of Δβ at 0.242 nm are used to calculate ΔE, 3.00 eV for C–C, 2.49 eV for C–O and 2.00 eV for O–O [9]. Eq. (4) indicates that ΔE is large when $|E^*_a - E^*_b|$ is small. Hence, $|E^*_a - E^*_b|$ is an index of the strength of adsorptive interaction on the adsorbent surface.

3) Three-body Interaction Model

It is very difficult to estimate a strict three-body interaction of adsorbate, adsorbent and water [9]. We propose a simplified model based on the superposition of two–body interactions. Fig. 5 shows the model for three body-interaction. Only adsorbate and water interact with each other and are stabilized by the HOMO-LUMO interaction before adsorption as shown in Fig. 5(a). In this case, we assume that the principle of superposition can be applied to the calculation of the total stabilization energy E_a. Assuiming that the total stabilization energy E_a is given as $\Delta E^{ac}+\Delta E^{ca}$, that is the sum of the maximum perturbation energy ΔE^{ac} and ΔE^{ca} by HOMO-LUMO interactions.

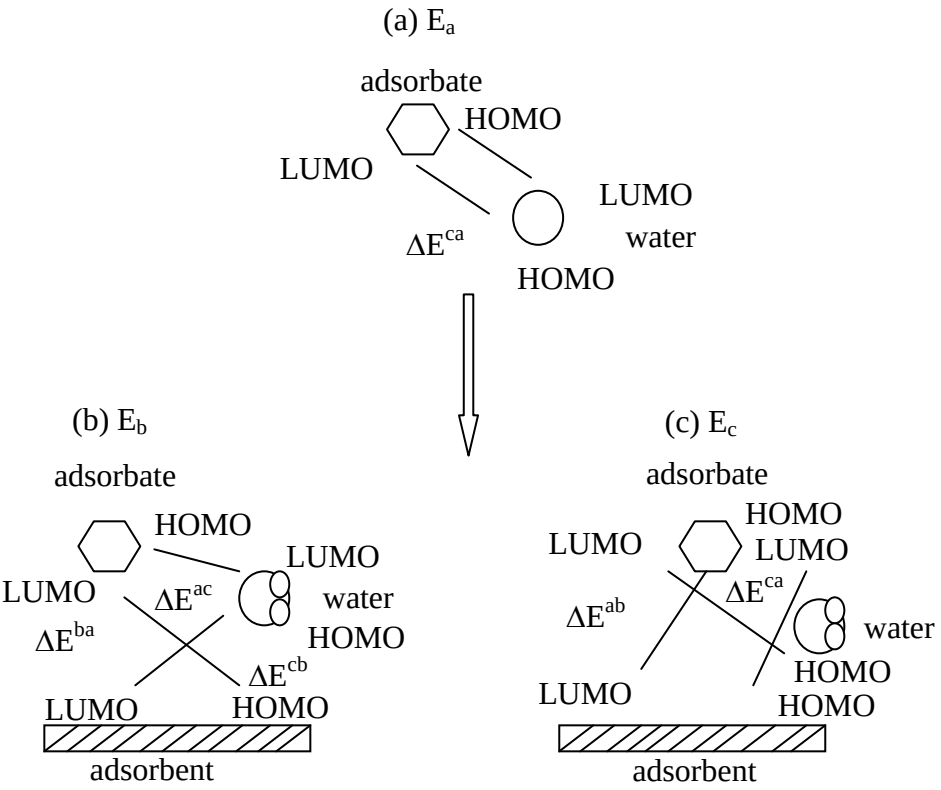


Fig. 5 Three body interaction model

In case of adsorption, we consider the following two cases.

Case 1: The adsorbate acts as an electron acceptor for the adsorbent as shown in Fig. 5(b). We assume that, according to the principle of superposition, the total stabilization energy, $E_b = \Delta E^{ac}+\Delta E^{cb}+\Delta E^{ba}$

Case 2: The adsorbate acts as an electron donor for the adsorbent as shown in Fig. 5(c). Assuiming that the total stabilization energy E_c is given as $E_c= \Delta E^{ab}+\Delta E^{bc}+\Delta E^{ca}$.

The larger stabilization energy between E_b and E_c gives the adsorption state. We regard the larger energy difference between E_b-E_a and E_c-E_a as the characteristic energy for the adsorption in aqueous solution ΔE_{ad}.

In aqueous solution water forms a structure by hydrogen bonding and it is very difficult to execute the MO calculation. The ab initio MO calculation for super molecules is required to evaluate the accurate adsorption energy and the adsorption geometry. In this work we use semiempirical MO calculation, the frontier orbital theory and the simplified interaction model and we cannot obtain information on the adsorption geometry. Since, characteristic energy ΔE_{ad} estimated by the crude theoretical consideration is not equal to the absolute value of adsorption energy, but represents an index for the strength of adsorptive interaction in aqueous solution.

III. RESULTS AND DISCUSSION

A. Adsorption Equilibrium

Typical adsorption isotherms measured for S and R-isomer of trans sobrerol on three chiral polymers are shown in Fig. 6 and Fig. 7 and the plots are not shown for other racemic compounds as the trends are similar. The adsorption isotherm of S and R-isomers of all racemic compounds could not be obtained in the same equilibrium concentration range of liquid phase due to high adsorption capacity of the adsorbents. Table 2 shows the values of the isotherm parameters of S and R-isomers of five racemic compounds adsorbed on three chiral polymers. The data shows that polymer 3 has q values greater than that for other two polymers and may be the most appropriate polymer for enantioselective adsorption of S-isomer of racemic drug molecules.

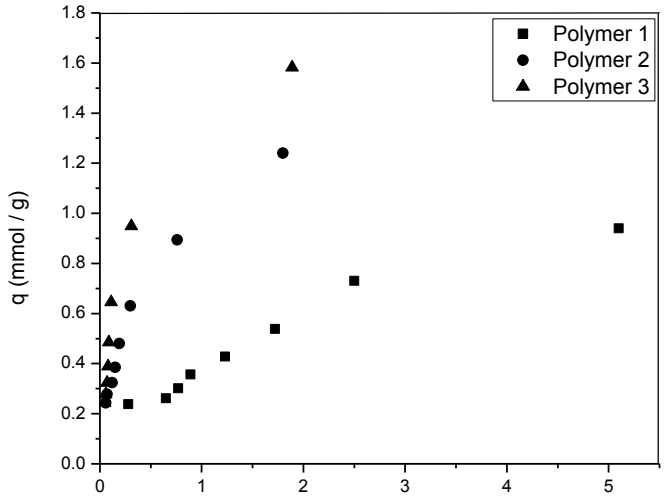


Fig. 6 Adsorption isotherm of S-isomers of Trans sobrerol on chiral polymer

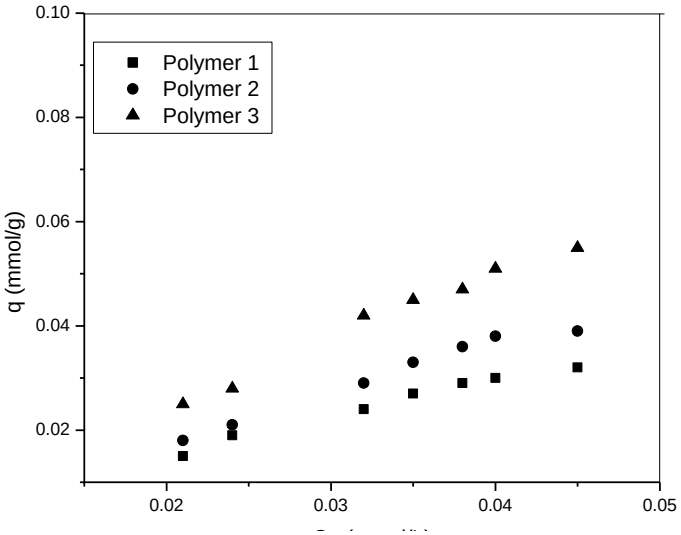


Fig. 7 Adsorption isotherm of R-isomers of Trans sobrerol on chiral polymer

TABLE 2 PARAMETER VALUES FOR THE ADSORPTION ISOTHERM OF R- AND S-ISOMER OF DIFFERENT RACEMIC COMPOUNDS ON CHIRAL POLYMERIC MEMBRANE

Polymer	Racemic compound	Langmuir model S-isomer R-isomer					
		K_S (mM^{-1})	X_{mS} (mM)	R^2	K_R (mM^{-1})	X_{mR} (mM)	R^2
Polymer 1	Propranolol Hydrochloride	2.1201	6.1930	0.9898	0.0312	198.7109	0.9729
	Atenolol	3.9159	6.7176	0.9751	0.0591	121.2791	0.9579
	Salbutamol	4.1242	6.1212	0.9719	0.0731	29.2192	0.9891
	Captopril	14.7912	5.9987	0.9987	2.2156	21.9134	0.9814
	Trans sobrerol	19.6284	0.7623	0.9933	4.1745	13.0293	0.9951

Polymer 2	Propranolol Hydrochloride	2.8401	6.0191	0.9798	0.0372	179.2193	0.9817
	Atenolol	4.7156	3.7951	0.9891	0.0671	160.2912	0.9729
	Salbutamol	4.9791	6.0112	0.9851	0.0829	34.13	0.9721
	Captopril	14.9894	5.9987	0.9852	1.2291	20.7561	0.9512
	Trans sobrerol	21.2712	0.7159	0.9721	3.9913	13.0091	0.9719
Polymer 3	Propranolol Hydrochloride	3.2700	5.4531	0.9952	0.0476	176.7801	0.9759
	Atenolol	5.0094	5.2462	0.9864	0.0710	60.9045	0.9875
	Salbutamol	5.9875	5.2030	0.9927	0.1855	18.9100	0.9751
	Captopril	16.5952	3.7329	0.9715	3.9105	16.2155	0.9743
	Trans sobrerol	27.2194	0.5194	0.9891	5.2193	12.2191	0.9834

The reasons for difference in adsorption of S and R-isomers of racemic compounds on different chiral polymers are not well understood. However, better adsorption of S-isomer on each polymer than that of R-isomer is due to the self association behavior as reported in our earlier publications [2-4]. It may be noted that adsorption could be affected by external physicochemical parameters such as pH, temperature, competing compounds present in the solution and on the chemical structure of chiral polymer or other characteristics such as porosity, adsorbent polarity, specific surface area and pore volume distribution. Surface area and pore radius keeps a linear relation with adsorption capacity with pore radius ≤ 90 Å [17]. In our study chemical nature of the adsorbent plays a more important role than the physical structure. In spite of the very bulky substituent, a high molecular weight polymer can form a tough membrane which has more adsorptive capacity than the other polymers. Different values of adsorption intensity of different polymers perhaps provide evidence on the adsorption mechanism, attributable to hydrophobic interaction, whereas the difference in values of adsorption intensity of different polymers may provide evidence of hydrogen bonding as the probable mechanism. In the adsorption system this type of behavior has also been reported by other researchers also for different systems [18].

B. Adsorption Isotherm

The adsorption equilibria were interpreted from Langmuir isotherm which is based on the assumptions [19]: adsorbate molecules are held at a fixed number of localized sites, each site can accommodate one single adsorbate molecule, adsorption energy is equal for all sites and neighboring adsorbate-adsorbate interactions are absent. Accordingly, single enantiomer complexation can be described as

$$q_{nR} = \frac{X_{mR} K_R C_{eR}}{1 + K_R C_{eR}} \tag{5}$$

$$\text{and} \quad q_{nS} = \frac{X_{mS} K_S C_{eS}}{1 + K_S C_{eS}} \tag{6}$$

where K (mM^{-1}) is the Langmuir affinity constant, C_e and q_n (mM) are the equilibrium concentration of bulk and bound enantiomers respectively. The indices R and S refer to the R and S enantiomers respectively. The Langmuir saturation constant X_m (mM) is the maximum attainable concentration of bound enantiomer. Table 2 shows the value of the isotherm parameters estimated by non-linear regression analysis. The value provides the most satisfactory representation of the experimental data almost at all experimental sets which confirm the enantioselective adsorption of the racemic compound on chiral polymer [3]. For aqueous phase adsorption on various adsorbents Langmuir, Freundlich and Redlich-Peterson isotherm models have been found to be satisfactory for various solutes such as β-lactam antibiotics, phenols and flavonoids etc. as reported in literature [13, 17].

The classification of adsorption isotherm of solutes from aqueous solutions depends on the configuration of the initial part of the isotherm and it gives the quasi qualitative information on the nature of the solute-surface interaction [20]. The adsorption isotherms obtained in this work are of the type L i.e. Langmuir class, with a linear initial part showing the high diffusion of solute into the adsorbent and suggests there is no strong competition between solvent and solute for occupation of the adsorption sites.

C. Adsorption Enthalpy

The temperature effect of the adsorption equilibrium was evaluated by measuring the adsorption at three different temperatures. Typical adsorption isotherm of different isomers of drug molecules on the chiral polymer 3 is shown in Fig. 8 and Fig. 9. In the figures, it appears that the adsorption intensity increases with decrease in temperature for both isomers. The enthalpy of adsorption was estimated from the Van't Hoff relation given by Eq. (3), in which the enthalpy was calculated from the temperature dependence of adsorption affinity. Fig. 10 and Fig. 11 shows typical Van't Hoff plot for adsorption of S and R-isomers of racemic compounds on chiral polymer 3 and the values of ΔH^o and q/C_e for the isomers in three polymers were shown in Table 3. The adsorbent which shows the highest affinity also shows the highest adsorption enthalpy. Similarly, the adsorbent exhibiting lowest affinity shows the lowest adsorption enthalpy. In this case different values of adsorption enthalpy are due to the difference in π-electron interactions between the chiral polymer and the isomers of the racemic compound. The π-electron interaction between chiral polymer and S-isomer is higher than that of R-isomer. Hence, adsorption enthalpy of S-isomer is higher in every case studied in this work. These values are more or less comparable with those values reported in literature for other systems [21-24].

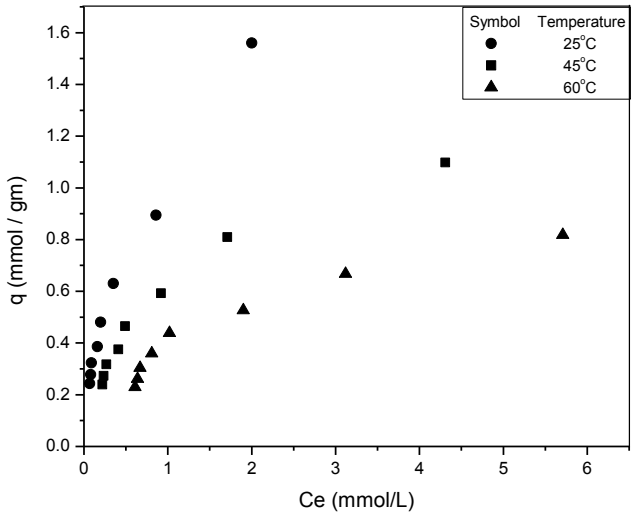


Fig. 8 Adsorption isotherm of S-isomer of Trans sobrerol on chiral polymer 3 as a function of temperature

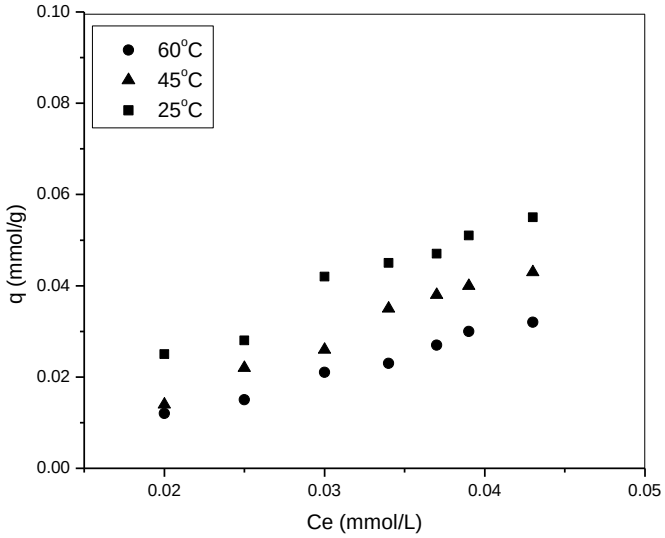


Fig. 9 Adsorption isotherm of R-isomer of Trans sobrerol on chiral polymer 3 as a function of temperature

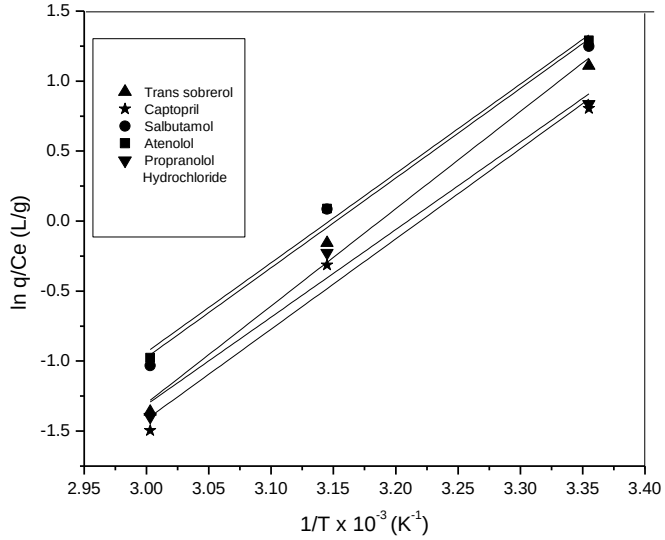


Fig. 10 Van't Hoff plot for S-isomers of racemic compound on polymer 3

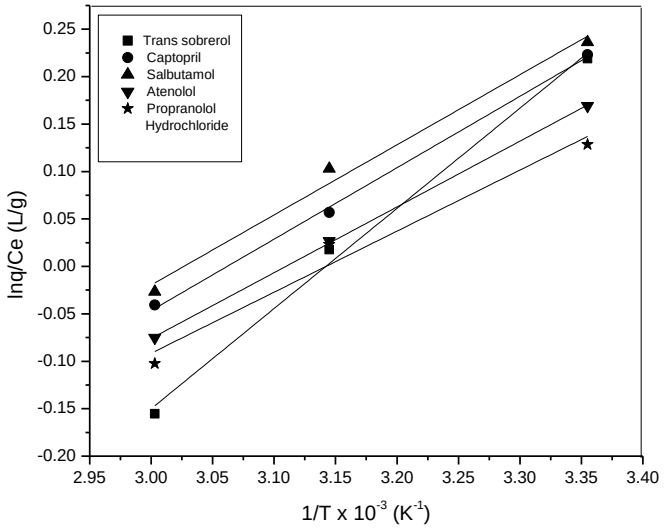


Fig. 11 Van't Hoff plot for R-isomers of racemic compound on polymer 3

TABLE 3 VALUES OF - ΔH^O AND Q/C_E OF R AND S-ISOMERS FOR RACEMIC COMPOUNDS ON DIFFERENT POLYMERS

Polymer	Racemic compound	q/C_e (l/g)		$-\Delta H^o$ (k J/mol)		R^2
		S-isomer	R-isomer	S-isomer	R-isomer	
Polymer 1	Propranolol Hydrochloride	0.7741	0.583	24.2695	2.9858	0.9729
	Atenolol	0.85	0.621	27.2160	3.2565	0.9951
	Salbutamol	1.0406	0.653	27.4986	3.9875	0.9920
	Captopril	2.0239	0.852	28.7011	4.3256	0.9832
	Trans sobrerol	2.554	0.885	30.8063	5.6325	0.9921

Polymer 2	Propranolol Hydrochloride	0.6372	0.665	32.0024	3.2154	0.9729
	Atenolol	0.8574	0.78	40.1711	4.3252	0.9954
	Salbutamol	1.1184	0.951	40.3557	5.2132	0.9949
	Captopril	1.6304	0.998	40.7964	5.8623	0.9853
	Trans sobrerol	4.2689	1.200	41.8762	6.1235	0.9910
Polymer 3	Propranolol Hydrochloride	1.4338	1.250	51.9835	5.3515	0.9776
	Atenolol	1.5937	1.279	53.0759	5.7614	0.9935
	Salbutamol	1.8679	1.307	53.2587	6.1439	0.9974
	Captopril	2.2647	1.382	53.5774	6.2612	0.9854
	Trans sobrerol	5.0791	1.400	57.7626	8.7806	0.9935

D. Correlation of Adsorptive Affinity with Interaction Energy

The adsorption affinity of polymer 3 is higher than that of other two polymers for all S and R-isomers of the drug molecules studied in this work. The adsorptive interaction energy between adsorbate and adsorbent ΔE, was calculated using Eq. (4) is correlated with adsorption affinity of S and R-isomer and shown in Fig. 12. The figure indicates a unique relationship between adsorptive affinity and adsorptive interaction for all racemic compounds tested in this work. The figure suggests that the equilibrium of adsorption is a strong function of the strength of the solute-sorbent binding interaction. Furthermore, a specific interaction between the aromatic ring of the sorbent and the planar region of the racemic drug molecule appears to play an important role in the adsorption process [22, 23]. This observation is similar to those obtained for adsorption of other compounds reported in literature [21-24].

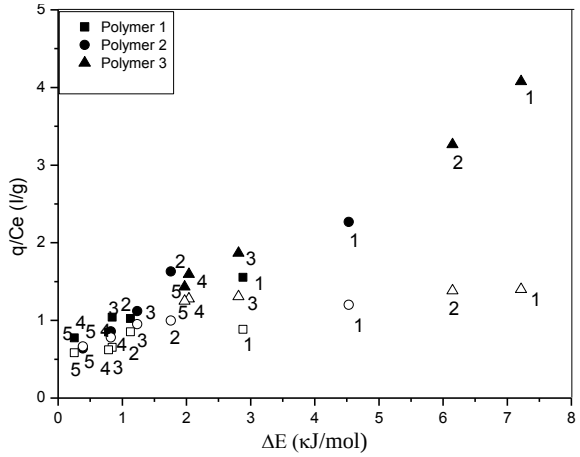


Fig. 12 Plot of adsorption affinity of R and S-isomer vs interaction energy
Open symbol: R-isomer, Closed symbol: S-isomer
1: Trans sobrerol, 2: Captopril, 3: Salbutamol, 4: Atenolol,
5: Propranolol Hydrochloride

Usually adsorption is affected by external physicochemical parameters such as pH, temperature, competing compounds present in solution, and on the chemical structure and other characteristic properties of the adsorbent such as particle size, porosity, polarity, specific surface area and pore volume distribution [25]. Surface area and pore radius keep a linear relation with adsorption capacity with pore radius ≤90˚A as reported earlier [25]. However, these parameters have not been explicitly considered for the interpretation of the correlation between adsorption affinity and interaction energy. It is noted that, for a given sorbent, adsorption is generally believed to result from two types of driving forces: specific driving forces resulting from solute–sorbent interactions

and depending on the sorbent surface chemistry, non-specific driving forces which are independent (or less dependent) of the surface and result primarily from solute–solvent interactions, which tend to drive organics from water (e.g. hydrophobic interactions). The solubility is affected by the solvophobicity of a compound, and the greater its solvophobicity with respect to a given solvent, the greater its tendency to be adsorbed from that solvent at interfaces with other phases [26]. However, in our study chemical nature of the adsorbents used plays more important role for adsorption of isomers. Chiral polymer 3, which gives the highest affinity for all the adsorbate molecules is a more bulky polymer than other two and is more efficient for adsorption of S-isomer of the racemic compounds due to its S-selectivity.

E. Correlation of Adsorptive Enthalpy with Interaction Energy

The values of adsorption enthalpy (ΔH°) for S and R-isomer obtained from Eq. (3) were plotted against adsorptive interaction energies (ΔE) and shown in Fig. 13, which shows a reasonable linear relationship. This implies that the enthalpies of adsorption are in conformity with adsorptive interaction energy. Since the enthalpy is a measure of the strength of the solute–sorbent binding interaction, the correlation shown in Fig. 13 demonstrates that the strength of the solute – sorbent binding interaction significantly affects the adsorption affinity and the process may be considered to be of enthalpic type.

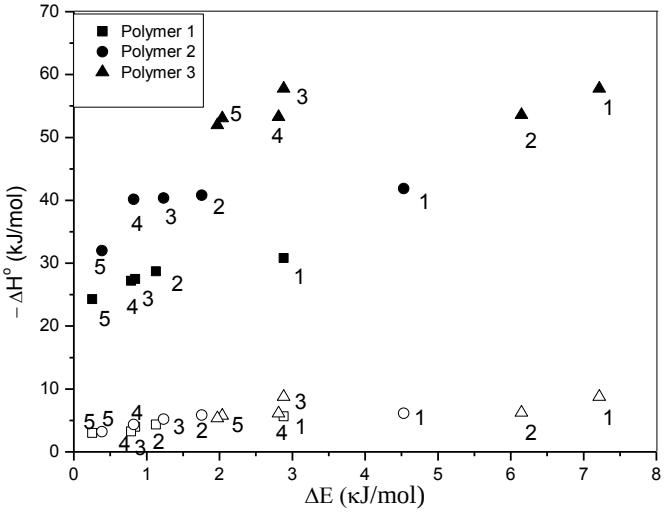


Fig. 13 Plot of adsorption affinity of R and S-isomer vs interaction energy
Open symbol: R-isomer, Closed symbol: S-isomer
1: Trans sobrerol, 2: Captopril, 3: Salbutamol, 4: Atenolol,
5: Propranolol Hydrochloride

F. Correlation of Selectivity with Interaction Energy

Chiral polymers are preferentially allowing a specific enantiomer to adsorb to or diffuse. This specificity is generated by chiral recognition sites in the polymer such as chiral side chains, chiral backbones, or immobilized chiral selectors. These polymers may act as selective barriers due to the stereospecific interaction between the enantiomer and chiral recognition sites [27].

In the adsorption process of chiral polymers the sorption coefficient is a thermodynamically determined parameter defined as the ratio of the concentration in the polymer to that in the solution. Hence, the selectivity of the polymer can be calculated from the concentration of the isomers in the solution. i.e.

$$\alpha = C(\mathrm{R})/C(\mathrm{S}) \text{ or } C(\mathrm{S})/C(\mathrm{R}) \tag{7}$$

where C(R) and C(S) are the concentrations of the R-enantiomer and S-enantiomers, respectively in the solution.

The selectivity of the polymer obtained from Eq. (7) is plotted against interaction energy which gives a straight line as shown in Fig. 14. This implies that the selectivity is in conformity with adsorptive interaction energy. The correlation shown in Fig. 14 demonstrates that the strength of the isomer–polymer binding interaction significantly affects the adsorption process of the chiral polymer.

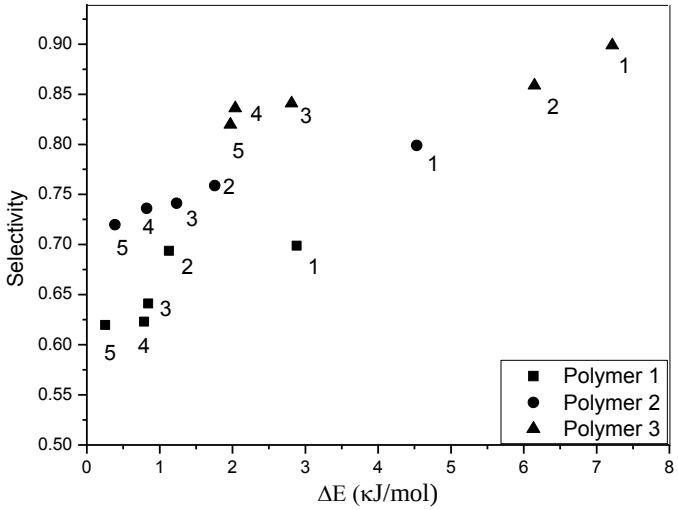


Fig. 14 Plot of selectivity of adsorption versus interaction energy
1: Trans sobrerol, 2: Captopril, 3: Salbutamol, 4: Atenolol,
5: Propranolol Hydrochloride

IV. CONCLUSION

The adsorption of five racemic drug molecules on three different chiral polymers was studied and experimental data were interpreted from Langmuir model for single enantiomer complexation. Out of three polymers one chiral polymer provides higher adsorption intensity of S-isomer due to self association behavior. Adsorption interaction energies between isomers of racemic compound and chiral polymers were calculated using frontier orbital theory. The computational and experimental studies described in this paper provide further insight into the mechanisms by which S and R-isomer of racemic compound bind to the surface of chiral polymer. These theoretical results show good correlations with experimental results on adsorption affinity and enthalpy. The results have stimulated the development of alternative sorbents which confer high selectivity and capacity for liquid phase adsorption of individual isomers by limiting adsorption to specific interactions. The development of such sorbents has been greatly facilitated by advances in chiral polymer synthesis methods, which has made it possible to produce polymeric sorbents of well characterized and uniform chemical surfaces. Accordingly, these results are expected to provide implication for sorbent surface modification and better design of adsorbents with high selectivity and capacity for liquid phase adsorption of different isomers of drug molecule.

REFERENCES

[1] M. M Bora, A. C. Ghosh and N. N. Dutta, "Reactive Extraction of 6- Aminopenicillanic Acid using Aliquot-336: Equilibrium and Kinetics," *Can. J. Chem. Eng.*, vol. 75, pp. 520-526, 1997.

[2] S. Hazarika, "Enantioselective Permeation of Racemic Alcohol through Polymeric Membrane," *J. Mem. Sci.*, vol. 310, pp. 174-183, 2008.

[3] S. Hazarika, S. Borthakur, P. G. Rao and N.N. Dutta, "A Novel Method for Preparation of Chiral Polymer Useful for Membrane Application," *Polymer Journal*, vol. 41(2), pp.1067-107, 2009.

[4] S. Hazarika, N.N. Dutta and P.G. Rao, "A Quantitative Structure Activity Relationship Study on Permeation of Amino acids in Enantioselective Membranes," Appl. Mem. Sc. & Technol, vol. 2, pp. 13-29, 2006.

[5] X. Rui, Y.C. Liang and G.D. Jin, "Membranes and Membrane processes for chiral Resolution," Chem. Soc. Rev. 2008, vol. 37, pp. 1243-1263.

[6] R. Couture, R. Rouseff, "Debittering and deacidifying sour orange (*Citrus auarantium*) juices using neutral and anion exchanger resin," *J. Food Sci.*, vol. 57, pp. 380-384, 1992.

[7] A. W. Trochimczuk, M. Streat, B. N. Kolarz, "Adsorptive properties towards phenol and its derivatives," *React. And Funct. Polym*, vol. 46, pp. 259-271, 2001.

[8] R L. Johnson, B. V. Chandler, "Adsorptive removal of bitter prin- ciples and tritratable acid from citrus," *Food Technol*., vol. 42, pp. 130-137, 1988.

[9] H. Tamon, K. Aburai, M. Abe, M. Okazaki, "Interpretation of Adsorptive Interaction in Aqueous Solution by Frontier Orbital Theory," *J. Chem. Eng. Jpn*, vol. 28, pp. 823-829, 1995.

[10] K. Fukui, T. Yonezawa, H. Shingu, "A Molecular Orbital Theory of Reactivity in Aromatic Hydrocarbons," *J. Chem. Phys.*, vol. 20, pp. 722-725, 1952.

[11] L Salem, "Intermolecular Orbital Theory of the Interaction between Conjugated Systems," *Physical and Inorganic Chemistry*, vol. 90(3), pp. 543-552, 1968.

[12] M. Dutta, N.N. Dutta, K.G. Bhattacharya, "Aqueous Phase Adsorption of Certain Beta-Lactam Antibiotics on to Polymeric Resins and Activated Carbon," *Sep. Purif. Technol*., vol. 16, pp. 213-224, 1999.

[13] A. Seidel, E. Tzscheutschler, K.H. Radeke, D. Gelbin, "Adsorption Equilibria of Aqueous Phenol and Indol Solutions on Activated Carbons," *Chem. Eng. Sc.*, vol. 40, pp. 215-222, 1985.

[14] Y. Otake, N. Kalili, T.H. Chang, E. Furuya, "Relationship between Freundlich Type Equation Constant and Molecular Orbital Properties," *Sep. Purif. Technol.*, vol. 39, pp. 67-72, 2004.

[15] K.L. Mardis, A.J. Glemza, B.J. Brune, G.F. Payne, M.K. Gilson," Differential Adsorption of Phenol Derivatives onto a Polymeric Sorbent: a Combined Molecular Modeling and Experimental Study," *J. Phys. Chem. B*, vol. 103, pp. 9879-9887, 1999.

[16] M. Scordino, A. Di Mauro, A Parrerine, E. Maccarone, "Adsorption of flavonoids on resins: hesperidin," *J. Agric. Food Chem*, vol. 51, pp. 6998-7004, 2003.

[17] D M Ruthven, "Principles of adsorption and adsorption processes," *New York: John Wiley & Sons*, pp. 210, 1984.

[18] P Gogoi, N. N. Duta, P G Rao, "Adsorption of Catechin from aqueous solutions on Polymeric resin and Activated Carbon," *Indian Journal of Chemical Technology*, vol. 17, pp. 337-345, 2010.

[19] A. Dabrowski, P. Podkoscielny, Z. Hubicki, M. Barczak, "Adsorption of Phenolic Compounds by Activated Carbon-A Critical Review," *Chemosphere*, vol. 58, pp. 1049-1070, 2005.

[20] C.A. Hunter, "Interactions Between Aromatic Systems: Do They Depend on Electrostatic Forces or Charge Transfer Transitions," *Angewandle Chemie*, vol. 105, pp. 1653-1655, 1993.

[21] M. Dutta, N. N. Dutta, KG. Bhattacharyya, "Adsorption Interaction of Certain Beta-Lactam Antibiotics in Aqueous Solution: Interpretation by Frontier Orbital Theory," *J. Chem. Eng. Jpn*., vol. 33(2), pp. 303-307, 2000.

[22] M.V. Chaubal, G F Payne, C H Reynolds, R L Albright, "Equilibrium for the Adsorption of Antibiotics onto Neutral Polymeric Sorbents: Experimental and Modeling Studies," *Biotechnol. Bioeng*., vol. 47, pp. 215-226, 1995.

[23] N. Maity, G.F. Payn, M.V. Ernest. Jr., R.L. Albright, "Caffeine Adsorption from Aqueous Solutions onto Polymeric Sorbents: the Effect of Surface Chemistry on the Adsorptive Affinity and Adsorption Enthalpy," *Reactive Polym*., vol. 17, pp. 273-287, 1992.

[24] E.M. Silva, D.R. Pompeu, Y. Larondelle, H. Rogez, "Optimisation of the Edulis Leaves on Macroporous Resins Using an Experimental Design Methodology," *Sep. & Purif. Technol.*, vol. 53 pp. 274-280, 2007.

[25] I.A .Huxam, B. Rowatt, "Characterization of Macroporous Polystyrene and Relationship to the Adsorption of Cephalosporin – C," *Macromol. Chem*., vol. 192, pp. 1695-1703, 1991.

[26] G.F Payne, N. N. Payne, Y. Ninomi, M.L. Shuler, "Adsorption of Non Polar Solutes onto Neutral Polymeric Sorbents," *Sep. Sci. Technol*., vol. 24, pp. 457-465, 1989.

[27] A. Higuchi, M. Tamaid, Y-A Koe, Y-L TagawadI, Y-H Wuf, B-D Freemanf, J-T Bingg, Y Changh, Q-D Lingce, "Polymeric Membranes for Chiral Separation of Pharmaceuticals and Chemicals," *Polymer Reviews*, vol. 50(2), pp. 113-143, 2010.