Measurement of serum enzyme levels has provided a powerful tool for studies of hepatoxicity[21]. Treatment with BG (100 mg/kg and 300 mg/kg) significantly prevented ($P<0.001$) rise in the levels of SGPT, SGOT, ACP and ALP as compared with control group. The comparative histopathological studies of liver from different groups further corroborated the hepatoprotective efficacy of BG. On the basis of results obtained in the present investigation it can be concluded that BG exerts hepatoprotective activity and may serve as a useful adjuvant in several clinical conditions associated with liver damage.

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REFERENCES

1. Latha, U., Rajesh, M.G. and Latha, M.S. **Indian Drugs**, 1999, 36, 470.
2. Fulzele, S.V., Satturwar, P.M., Joshi, S.B. and Dorle, A.K., **Indian Drugs**, 2002, 39, 42.
3. Shah, E., **US Patent** No. US5693327, 1997.
4. Oyebola, D.D., **Afr. J. Med. Med. Sci.**, 1983, 12, 57.
5. Khanuja, S.P.S., **US Patent** No. US 6410059, 2002.
6. Malhotra,C.L. and Das, P.K., **Indian J. Med. Res.**, 1959, 47, 244.
7. Prakash, J.C. and Sirisi , M., **J. Sci. Ind. Res.**, 1962, 21, 93.
8. Singh, H.K. and Dhawan, B.N., **Indian J. Pharmacol.**, 1997, 29, S359.
9. Sumathy, T., Subramanian, S., Govindaswamy, S., Balakrishna, K. and Veluchamy, G., **Phytother. Res.**, 2001, 15, 643.
10. Tripathi, Y.B., Chaurasia, S., Tripathi, E., Upadhyay, A. and Dubey, G.P., **Indian J. Exp. Biol.**, 1996, 34, 523.
11. Wetton, P., Eds. In; British Herbal Pharmacopoea, The British Herbal Medicine Association, London, 1996, 50.
12. Panchal, G.N. and Bhatt, H.V., **Indian J. Exp. Biol.**, 1989, 27, 561.
13. Yoshikawa, M., Hatakeyama, S., Inoue, Y. and Yamahara, J., **Chem. Pharm. Bull.**, 1993, 41, 214.
14. Chao, J.Y., Baik, K.V., Jung, J.H. and Park, M.H., **European J. Pharmacol.**, 2000, 398, 399.
15. Kulkarni, S. and Desai, S., **Indian J. Pharm. Sci.**, 2001, 63, 292.
16. Gupta, O.P. and Ghatak, B.J.R., **Indian J. Med. Res.**, 1967, 55, 1078.
17. Kirtikar, K.R. and Basu, B.D., Eds., In; Indian Medicinal Plants. Vol. III. International Book distributors Dehradun, 1998, 1737.
18. Reitman, S. and Frankel, S., **Amer. J. Clin. Path.** 1957, 28, 53.
19. Kind, P.R.N. and King, A.J., **J. Clin. Pathol.**, 1954, 7, 322.
20. Plaa, G.L., **Annu. Rev. Pharmacol. Toxicol.**, 2000, 40, 42.
21. Buwa, S., Patil, S., Kulkarni, P.H. and Kanase, A., **Indian J. Exp. Biol.**, 2001, 39, 1022.

Surface Activity of Cox-2 inhibitors

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Surface tension of four cox-2 inhibitors, celecoxib, rofecoxib, meloxicam and nimesulide has been determined at 20°. Surface activity has been expressed in terms of surface pressure, surface excess and the area occupied on the liquid surface per drug molecule. Rofecoxib was not found to be surface active. Amongst other drugs, surface activity varied as nimesulide< meloxicam<celecoxib. Data was found to be in agreement with the octanol-water partition coefficients and polar surface area of drugs for all drugs except rofecoxib. Rofecoxib was exceptional in having small partition coefficient and small surface activity in spite of a very small polar surface area.

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Non-steroidal antiinflammatory drugs (NSAIDs) play a major role in the management of inflammation and pain through the inhibition of prostaglandin synthesis by blocking cyclooxygenase (cox) activity[1-2]. Cyclooxygenase is known to exist in two isoforms; cox-1 and cox-2. Under the influence of cox-1, prostaglandins maintain the integrity of the gastric mucosa, mediate normal platelet function and regulate renal blood flow. Cox-2 is induced in inflammatory cells when they are activated and is responsible for production of prostaglandins that mediate inflammation, pain and fever[3-4]. Thus the side effects of NSAIDs can be avoided by using specific drugs acting selectively on the cox-2 isoform. Physico-chemical properties of drugs are of great interest to understand drug action at the molecular level since physico-chemical and physiological properties are interrelated. Surface activity of drugs is of particular relevance in relation to the solubility and permeability of drugs across biological barriers[5-6]. Present paper reports surface activity of four cox-2 inhibitors; celecoxib, rofecoxib, meloxicam and nimesulide. Such studies for the cox-2 inhibitors used in the present work have not been reported so far.

Rofecoxib and celecoxib were obtained as gift samples from M/s Ranbaxy Research Laboratories, Gurgaon. Meloxicam and nimesulide were also gift samples from M/s Sun Pharmaceuticals Industries Ltd., Mumbai and Panacea Biotec Ltd., Lalru, respectively. All solvents were of analytical grade. They were first dried by keeping in contact with Linde type 4A molecular sieves overnight. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were further purified by distillation under reduced pressure. Acetonitrile (ACN) was refluxed with 1% (w/v) phosphorus pentoxide for half an hour and then distilled. Water used was double distilled in all glass apparatus.

Surface tensions of drug solutions were measured in an air thermostat at 20° using a stalagmometer by drop number method[7]. Densities of solutions were measured by making use of an Austrian precision density meter (Anton Paar, model DMA 60 attached to external measuring cell, DMA602 with an 8-decimal place digital period meter with selectable precision). Due to poor aqueous solubility of the selected drugs, some preliminary experiments were carried out to determine the minimum concentration of non-aqueous solvent required for dissolution of drug. On the basis of these experiments, the solvents employed were 10% aqueous DMSO for rofecoxib, 10% aqueous DMF for meloxicam and 20% aqueous ACN for celecoxib and nimesulide and the concentration range was varied from 20-60 µg/ml for celecoxib, rofecoxib and meloxicam and 60-100 µg/ml for nimesulide.

The surface activity is a consequence of the amphipathic nature of drugs. The hydrophobic portion of the drug molecules is, in general more complex than those of typical surfactants, often being composed of aromatic or heterocyclic ring systems. The surface activity depends on the nature of the hydrophobic and hydrophilic portions of the drug molecule. Such studies on local anaesthetic and antipsychotic drugs have been reported by Zografi and Munshi[5]. Recent studies have shown that the surface activity measurements form the basis of a fast and simple technique to reliably predict the ability of a drug to cross the blood brain barrier[6].

Surface tension data at different drug concentrations was used to calculate various parameters related to surface activity of drugs. Results are expressed in terms of surface pressure (π), surface excess (Γ_2) and the area occupied on the liquid surface per drug molecule (A). These parameters were calculated using Eqns. 1-3. $\pi=\gamma_{solvent}-\gamma_{solution}$ (Eqn. 1), $\Gamma_2 = -1/RT(d\gamma/d \ln C_2)$ (Eqn. 2) and $A=1/(N_A\Gamma_2)$ (Eqn. 3), where γ is the surface tension, C_2 is the drug concentration in moles per liter and N_A is the Avogadro's number. The term $d\gamma/d \ln C_2$ in the Gibb's adsorption equation (Eqn. 2) was obtained from the slope of the linear γ versus $\ln C_2$ plots, shown in fig. 1. The linearity of the plots showed that the drug concentrations used are below the critical micellar concentrations[8]. In the linear region, the drug molecules are closely packed at the surface and the area occupied per molecule is constant[8]. The area occupied per molecule could therefore, be calculated by use of Eqn. 3. The values for various parameters are given in Tables 1 and 2.

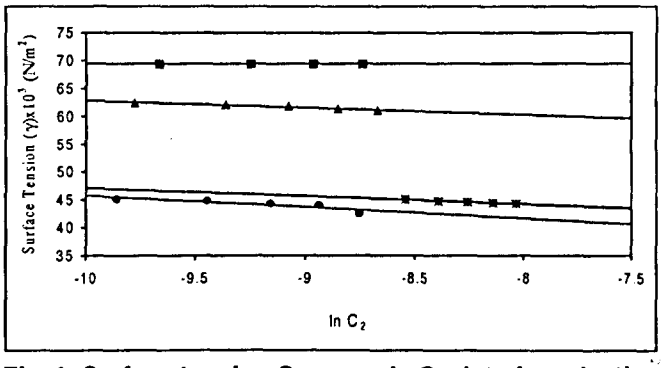

Fig. 1: Surface tension O versus ln C_2 plots for selective cox-2 inhibitors.

C_2 is the molar concentration of drug. Celecoxib (-●-), rofecoxib (-■-), meloxicam (-▲-) and nimesulide (-ς-).

TABLE 1: SURFACE PRESSURE OF DRUGS AT DIFFERENT CONCENTRATIONS

Surface Pressure(π)x10^3 (N/m)					
Concentration (μg/ml)	Celecoxib	Rofecoxib	Meloxicam	Concentration (μg/ml)	Nimesulide
20	0.316	0.000	0.338	60	0.624
30	0.627	-0.001	0.628	70	0.932
40	1.084	-0.002	0.908	80	1.085
50	1.385	-0.003	1.578	90	1.234
60	2.932	-	1.759	100	1.384

Surface pressure (π) was calculated from surface tension data at 20° using equation 1.

TABLE 2: SURFACE ACTIVITY PARAMETERS FOR VARIOUS DRUGS

Drug	Surface Pressure (π) x 10^{3*} (N/m)	Surface Excess ((Γ_2)x10^7 (mol/m^2)	Area/molecule (A) ((nm)^2/molecule)
Celecoxib	2.932	8.36	1.99
Meloxicam	1.759	5.43	3.10
Nimesulide	0.624	5.93	2.80

*Reported surface pressure values are at a drug concentration of 60:g/ml. Various parameters have been calculated using equations 1-3.

The relative surface activity of various drugs at different concentrations was compared using surface pressure data given in Table 1. Rofecoxib was not found to be surface active; rather the surface pressure had a small negative value. Amongst other drugs, surface activity varied as nimesulide<meloxicam<celecoxib. Surface pressure values at a drug concentration of 60 μg/ml are also given in Table 2 along with other parameters. The surface excess (Γ_2) varied from 5.43x10^{-7} to 8.36x10^{-7} mol/m^2 and the area occupied on the surface per molecule varied from 2.80 to 1.99 (nm)^2 for various drugs. These parameters are useful indicators of the hydrophobicity of drug molecules. Since hydrophobicity of the drug is a major factor responsible for drug-receptor interactions in biological systems, such studies can contribute significantly.

Two other properties related to surface activity, octanol partition coefficients (log P) and polar surface area (PSA) of drugs have also been calculated using software molinspiration[9]. Log P and PSA values, given in Table 3, are in agreement with the surface activity data. Partition coefficients decrease in the order celecoxib>meloxicam> nimesulide>rofecoxib and polar surface areas increase in the order rofecoxib<celecoxib<meloxicam<nimesulide. In the case of celecoxib, meloxicam and nimesulide, the surface activity is directly proportional to partition coefficient and inversely proportional to the polar surface area, as expected. Rofecoxib is, however, exceptional in having small partition coefficient and small surface activity in spite of a very small polar surface area.

TABLE 3: OCTANOL-WATER PARTITION COEFFICIENTS AND POLAR SURFACE AREA OF VARIOUS DRUGS

Drug	Partition Coefficient* (log P)	Polar Surface Area* (PSA)
Celecoxib	3.683	77.991
Rofecoxib	1.705	60.447
Meloxicam	1.904	99.598
Nimesulide	1.788	101.227

*Reported values have been calculated using software Molinspiration[9].

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REFERENCES

1. Allison, M.C., Howaston, A.G., Torans, C.J., Lee, F.D. and Russel, R.I., **N. Engl. J. Med.**, 1992, 327, 749.
2. Rodriguez, G.L.A. and Jick, H., **Lancet**, 1994, 343, 769.
3. Hawkey, C.J., **Lancet**, 1999, 353, 307.
4. Silas, S. and Clegg, D.O., **Bull. Rheum. Dis.**, 1999, 40, 1.
5. Zografi, G. and Munshi, M., **J. Pharm. Sci.**, 1970, 59, 819.
6. Seelig A., Gottschlich, R. and Devant, R.M., **Proc. Natl. Acad. Sci. USA**, 1994, 91, 68.
7. Jain, D.V.S. and Singh, S., **Indian J. Chem.**, 1972, 10, 629.
8. Schott, H., **J.Pharm. Sci.**, 1980, 69, 852.
9. Seedher, N. and Aggarwal, S., **Indian J. Pharm. Sci.**, 2003, 65, 53.