Both granular and tablet properties were evaluated and compared with the results obtained by using thermally heated starch paste. The dissolution rate has been enhanced from the tablets prepared by using HTGS as binder. Due to its stability, HTGS may be preferred over conventional starch paste.

REFERENCES

1. Neuberg, C., **Biochem. J.**, 1916, 76, 107.
2. Miyahara, M. and Takahasi, T., **Chem. Pharm. Bull.**, 1982, 30, 288.
3. Hamaza, Y.E. and Paruta, A.N., **Drug Dev. Ind. Pharm.**, 1985, 11, 1577.
4. Badman, A.A., Khordagui, L.K., Saleh, A.M. and Khail, S.A., **Int. J. Pharm.**, 1983, 13, 67.
5. Jain, N.K. and Patel, V.D., **Indian Drugs**, 1996, 32, 160.
6. Feigen, G.A. and Trapini, I.L., **Arch. Biochem. Biophys.**, 1988, 40, 25.
7. Saheh, A.M., Ghaly, G.M. and Darwish, I.A., **J. Pharm. Sci.**, 1987, 1, 90.
8. Khordagui, L.K., Salesh, I.K. and Khatil, A.M., **Int. J. Pharm.**, 1980, 7, 111.
9. Wadke, D.A., Serajuddin, A.M. and Jacobason, H., In; Lieberman, H.A., Lachman, L. and Schwarty, J.B. Eds., Pharmaceutical Dosage Form: Tablets, Vol. 1, 2nd Edn., Marcel Dekker INC.
10. Indian Pharmacopoeia, 4th Edn., Controller of publications, New Delhi, 1996, 736.
11. Indian Pharmacopoeia, 4th Edn., Controller of publications, New Delhi, 1996, A-80.
12. Banker, G.S. and Anderson, N.R. In; Lachman, L., Lieberman, H.A. and Kanig, J.L. Eds., The Theory and Practice of Industrial Pharmacy, 3rd Edn., Varghese Publishing House, Mumbai, 1991, 299.

Role of Skin Cholesterol in Permeation of Indomethacin

ANAND, O., GUPTA, S. AND TIWARY, A.K.*

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala-147 002

Accepted 11 January 2001

Revised 19 December 2000

Received 21 February 2000

The possible role of skin cholesterol in modifying the percutaneous permeation of indomethacin was studied by employing lovastatin, an inhibitor of cholesterol synthesis. The decreased cholesterol content of solvent perturbed skin was maintained till 24 h by topical application of lovastatin (1.125 mg/cm^2). Solvent perturbed-lovastatin treated viable skin excised after 24 h produced enhanced *in vitro* permeation of indomethacin. The time for 75% reduction in edema was significantly less in rats with perturbed-lovastatin treated skin as compared to that with normal skin.

The permeability barrier properties of skin are mediated by a series of extra cellular lipid multi-layers enriched in fatty acids, ceramide and cholesterol. When the barrier is perturbed by removal of these lipids, a sequence of biological response is initiated that accelerates epidermal synthesis of these lipids[1-3] in a bid to restore the barrier status of skin. Cholesterol synthesis is reported to be mainly responsible for the early phase of epidermal barrier repair[4]. Hence, the role of lovastatin (LVN), a competitive inhibitor of HMG-CoA reductase in enhancing the percutaneous permeation of indomethacin (IDN), a highly lipophilic drug with low transcutaneous permeation[5,6] was investigated.

Lovastatin (Ranbaxy, New Delhi) and indomethacin (Jagsonpal, New Delhi) were gift samples. Cholesterol estimation kit was purchased from SPAN Diagnostics (Surat, India). Dorsal hairs of Wistar rats were removed by an electric razor and the skin excised after 24 h. Freshly excised skin was used for all experiments. Cholesterol (CHL) leaching ability of methanol-chloroform or acetone-

* For Correspondence

chloroform (2:1) was assessed by applying them (1.0 ml) to excised skin and mounting it on a Keshary-Chien diffusion cell filled with phosphate buffer (pH 7.4, 37°). Buffer was stirred at 300 rpm and withdrawn at various time intervals. CHL leached into the buffer was estimated by concentration under vacuum followed by treatment with cholesterol estimation kit. Similarly, CHL content of perturbed viable skin treated with LVN (0.75 and 1.125 mg in PEG 200/cm^2) was determined for assessing the efficacy of LVN in preventing *de novo* synthesis of CHL till 24 h. Skin portion was excised, dried to constant weight (50°), extracted by Folch method and CHL analyzed by using cholesterol estimation kit. *In vitro* permeation of IDN was studied using excised portion of normal, solvent perturbed or perturbed-LVN treated viable skin. Phosphate buffer (pH 7.4) at 37° containing PEG 200 (5% v/v) and 40% v/v solution of formaldehyde, for sink condition and preservation, respectively was stirred at 300 rpm. Samples were analyzed at 319 nm[8].

Anti inflammatory efficacy was determined by assessing the reduction of carrageenan-induced edema in rats. Four groups, each consisting of five rats received the following treatments: Group I, control; Group II, IDN (62.2 mg); Group III, IDN (62.2 mg) + LVN (0.75 mg/cm^2); Group IV, IDN (62.2 mg) + LVN (1.125 mg/cm^2). CHL in blood collected from tail vein of rats at 12 h was analyzed as an indicator of systemic absorption of LVN.

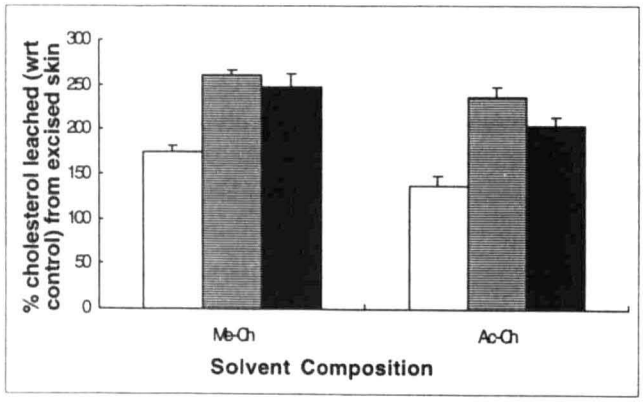

Fig. 1: Cholesterol leaching ability of solvents on excised rat skin.
Rat skin was treated with methanol-chloroform (2:1) or acetone-chloroform (2:1) for 5 min (□), 10 min (▤) or 15 min (■) and the % cholesterol leached from the skin into the receptor compartment was estimated.

Treatment of excised skin with a mixture of methanol-chloroform was found to be more effective than acetone-chloroform (2:1) in leaching CHL (fig.1). Scrubbing with methanol-chloroform for more than 10 min did not appreciably reduce the CHL content in viable skin (fig. 2). The CHL content of viable-perturbed skin returned to basal level by 6 h (fig. 3). This is due to a series of bio-

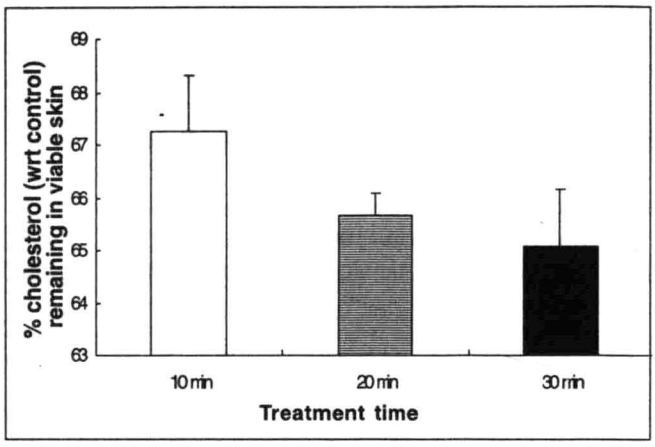

Fig. 2: Influence of treatment time on % cholesterol (wrt control) remaining in viable skin.
Methanol-chloroform (2:1) was applied to shaved dorsal skin of live rats. The animals were sacrificed at 10 min (□), 20 min (▤) or 30 min (■) and the cholesterol content in treated skin portion was determined.

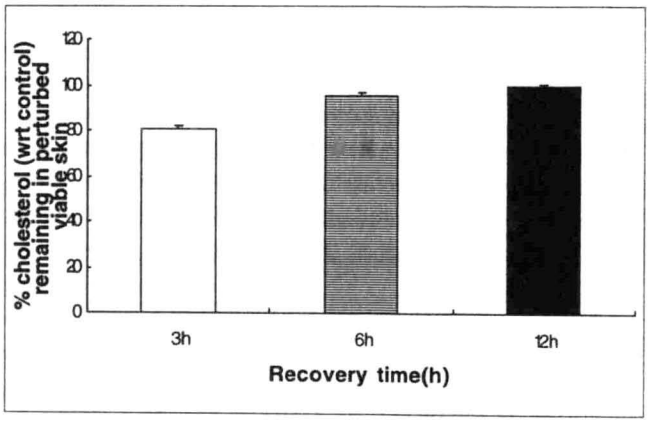

Fig. 3: Time dependent recovery of cholesterol in perturbed viable skin (wrt control).
Shaved dorsal skin of rat was treated with methanol-chloroform (2:1) for 10 min and then wiped with normal saline. The animals were sacrificed after 3 h (□), 6 h (▤) or 12 h (■) and the cholesterol content in treated skin portion was determined.

chemical reactions following perturbation effect[1-3,9,10]. The CHL content in LVN-treated (1.125 mg/cm²) perturbed skin after 24 h was almost same as that in freshly perturbed excised skin (fig. 4), indicating that *de novo* synthesis of skin CHL is inhibited by topical application of LVN.

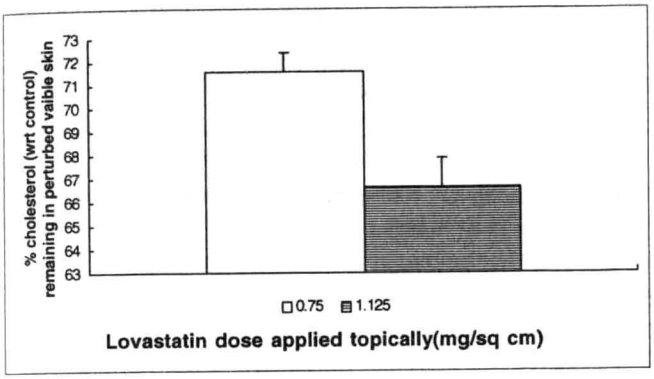

Fig. 4: Influence of lovastatin on cholesterol content in perturbed viable skin.
Lovastatin was applied to shaved skin of rat perturbed with methanol-chloroform at a dose of 0.75 mg/cm² (□) or 1.125 mg/cm² (▤). The animals were sacrificed after 24 h and the cholesterol content in treated skin portion was determined.

The *in vitro* permeation of IDN across perturbed-LVN-treated viable skin excised after 24 h was 5-fold more than that across normal skin. However, LVN did not produce a dose dependent enhancement of IDN permeation. Furthermore, the permeation of IDN across perturbed-LVN-treated viable skin excised after 24 h was lower than that across skin excised immediately after perturbation (Table 1). This seems to be due to the restrictions posed by enhanced synthesis of other constituents like ceramide and fatty acid in viable skin that are also regulated by barrier requirements[2,3].

The time for reduction of 75% edema (T_{75}) followed the order, Gr. I > Gr. II > Gr. III = Gr. IV ($p < 0.10$). This indicates that topical application of LVN to perturbed viable skin enhanced the systemic delivery of IDN (fig. 5). However, T_{75} for higher dose of LVN (Gr. IV) is not significantly different than that obtained with the lower dose. This result is in consonance with the result of *in vitro* permeation study where LVN treatment to perturbed viable skin did not produce a dose dependent enhancement. Furthermore, the blood CHL (at 12 h) decreased by 10% after the application of higher dose of LVN. Hence, there is a need for dose optimization of LVN for use as a

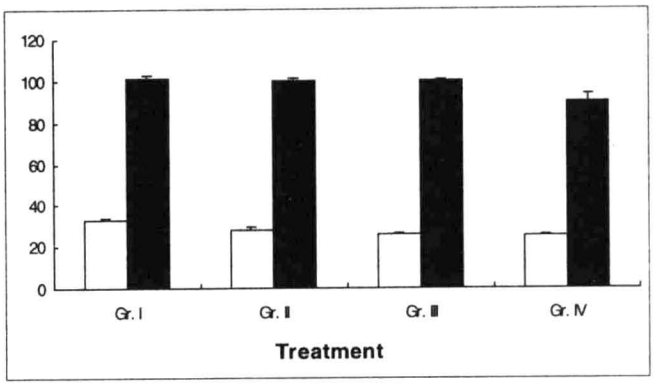

Fig. 5: Influence of various treatments on blood cholesterol and T_{75} for edema reduction.
Four groups, each consisting of five rats were given different treatments. Time for reduction of 75% (T_{75}) carageenan-induced edema (□) and blood cholesterol at 12 h (■) was determined.

TABLE 1 - *IN VITRO* PERMEATION OF INDOMETHACIN ACROSS RAT SKIN

Parameter	Treatment			Treatment		
	Control	Me-Ch (2:1)	Ac-Ch (2:1)	Control	LVN 1	LVN 2
Flux (mg/cm²/h)	6.39	50.98	45.86	7.98	35.55	37.40
Enhancement Ratio	1.0	7.97	7.17	1.0	4.45	4.68

In vitro permeation of indomethacin was measured across normal and solvent (Me, methanol; Ac, acetone; Ch, chloroform) perturbed rat skin and the influence of co-application of lovastatin at two different doses (LVN 1, 0.75 mg/cm²; LVN 2, 1.125 mg/cm²) to Me-Ch perturbed skin was determined.

percutaneous permeation enhancer. Nevertheless, the results of this investigation indicate a novel means of enhancing absorption of poorly permeable drugs.

REFERENCES

1. Proksch, E., Elias, P.M. and Feingold, K.R., **J. Clin. Invest.**, 1990, 85, 874.
2. Holleran, W.M., Feingold, K.R., Mao-Qiang, M., Gao, W.N., Lee, J.M. and Elias, P.M., **J. Lipid Res.**, 1991, 32, 1151.
3. Ottey, K.A., Wood, L.C., Grunfeld, C., Elias, P.M. and Feingold, K.R., **J. Invest. Dermatol.**, 1995, 104, 401.
4. Feingold, K.R., Mao-Qiang, M., Menon, G.K., Cho, S.S., Brown, B.E. and Elias, P.M., **J. Clin. Invest.**, 1990, 86, 1738.
5. Morimoto, K., Tojima, H., Haruta, T., Suzuki, M. and Kakemi, M., **J. Pharm. Pharmacol.**, 1996, 48, 1133.
6. Mikulak, S.A., Vangsness, C.T. and Nimmi, M.E., **J. Pharm. Pharmacol.**, 1998, 50, 153.
7. Folch, J., Lees, M. and Sloane-Stanley, G.H., **J. Biol. Chem.**, 1957, 226, 497.
8. Pharmacopoeia of India, Vol. 1, The Controller of Publications, Delhi, 1996, 393.
9. Menon, G.K., Feingold, K.R., Moser, A.H., Brown, B.E. and Elias, P.M., **J. Lipid. Res.**, 1985, 26, 418.
10. Grubauer, G., Feingold, K.R., Harris, R.M. and Elias, P.M., **J. Lipid. Res.**, 1989, 30, 89.

Enhancement of Dissolution Rate of Meloxicam

K.P.R. CHOWDARY* AND R. HYMAVATHI

Industrial Pharmacy Division, Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530 003

Accepted 11 January 2001

Revised 19 December 2000

Received 14 August 2000

Solid dispersions of meloxicam (MX) in polyvinyl pyrrolidone (PVP), hydroxy propyl methyl cellulose (HPMC), hydroxy propyl cellulose (HPC) and polyethylene glycol 6000 (PEG) and solvent deposited systems on lactose, soluble starch, microcrystalline cellulose (MCC), dicalcium phosphate (DCP), silica gel and their selected tablet formulations were investigated with an objective of enhancing the dissolution rate of MX. A marked enhancement in the dissolution rate and dissolution efficiency of MX was observed with all solid dispersions and solvent deposited systems. Among the carriers used in solid dispersions PVP gave highest enhancement (19 fold) in the dissolution rate of MX at 9:1 ratio of drug and carrier and in the case of solvent deposited systems MCC and DCP gave an improvement of 13.1 and 17.5 fold in the dissolution rate of MX respectively at 1:2 ratio of drug and excipient when compared to MX itself.The solid dispersions in PVP and HPMC and the solvent deposited systems on MCC and DCP could be formulated into tablets.These tablets, apart from fulfilling the official and other specifications, exhibited higher rates of dissolution and dissolution efficiency values.

Meloxicam[1] is an effective, new nonsteroidal antiinflammatory and analgesic drug. It is practically insoluble in aqueous fluids and its aqueous solubility was found to be 20 mg/l. The very poor aqueous solubility of the drug gives rise to difficulties in the formulation of dosage forms and may lead to variable dissolution rates

*For Correspondence