

results of the estimation and recovery studies are given in Table 1.

Our results have demonstrated that the developed method is simple sensitive, reproducible and the excipients contained in the formulation do not offer any interference in the determination. Hence, this method can be used for the routine analysis of the drug preparations.

## REFERENCES

1. Chang Z.L., Bauer, J.F., In; Florey, K. Ed., Analytical profiles of drug substances, Vol. 20 Academic Press, New York, 1991, 714.
2. Liu, Y.Z., *Yaowu Fenxi Zazhi*, 1993, 13, 410
3. Parimoo P., *J. Ind. Chem. Soc.*, 1987, 54, 562.
4. Parimoo P., Bharathi A., Padma K., *Indian Drugs*, 1996, 33, 160.
5. Parimoo P., Bindu, M.J., *Indian Drugs*, 1995, 32, 251.
6. Parimoo P., Balimani P.V. *Indian Drugs*, 1997, 34, 21.

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## Formulation and Evaluation of Polymeric Films of Indomethacin For Transdermal Administration

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Accepted 22 December 1997

Received 16 June 1997

Polymeric films of indomethacin were formulated employing ethyl cellulose and polyvinyl pyrrolidone as film formers and evaluated for transdermal administration. The *in vitro* percutaneous absorption of indomethacin through rat abdominal skin was dependent on film composition and initial drug loading dose. The films composed of EC:PVP:Drug (8:2:2 and 8:2:3) exhibited good anti-inflammatory activity over a period of 24 h. Significant ( $p < 0.01$ ) prevention of ulcerogenicity of indomethacin was observed by transdermal route compared to oral administration.

THE development of technology for the release of drugs at controlled rate to systemic circulation, using skin as port of entry, has become popular for various reasons<sup>1</sup>. The transdermal delivery of a drug to systemic circulation at a desired rate can be achieved by uniform distribution of drug throughout the polymer matrix<sup>2</sup>. The rate of drug release from these matrix diffusion-controlled transdermal drug delivery systems depends on the initial drug loading dose, solubility and diffusivity of drug in the polymer matrix. Further, the rate of drug release can be altered by changing the composition and dimensions of the polymer matrix<sup>3</sup>. The present investigation was carried out to study the influence of polyvinyl pyrrolidone (PVP) and initial drug loading dose on *in vitro* permeation of indomethacin through rat abdominal skin.

Further, the promising films were evaluated for their anti-inflammatory activity against carrageenan induced rat paw oedema model and ulcer index.

Ethyl cellulose (14cps, S.D Fine Chem), polyvinyl pyrrolidone (Ioba Chemie), dibutyl phthalate (Ranbaxy Laboratories Ltd.) Chloroform (HPLC grade, Qualligens), Carrageenan (Sigma Co., USA), Indomethacin (gift sample from M/s. Invinex Laboratories, Hyderabad).

The method of Munden *et al*<sup>4</sup> was adopted for the preparation of films. Dibutyl phthalate at a concentration of 30% w/w of dry polymers was used as plasticizer. The thickness of films was measured at five different places using a micrometer (MITOTOYO, Japan) and the mean

**Table 1. Influence of initial drug and PVP concentration on the permeation of indomethacin through rat abdominal skin**

Film composition EC : PVP: Drug	T <sub>lag</sub> (hr)	Permeation rate (mg/cm <sup>2</sup> .hr )	Film composition EC :PVP:Drug	T <sub>lag</sub> (hr)	Permeation rate (mg/cm <sup>2</sup> . hr)
10 : 0 : 1	2.45±0.29	0.0021± 0.0004	8:2:1	1.26± 0.21	0.0056± 0.0004
10 : 0 : 2	2.08± 0.31	0.0029 ±0.0005	8:2:2	1.38± 0.25	0.0069± 0.0007
9 : 1 : 1	1.63± 0.15	0.0033 ±0.0002	8:2:3	1.15± 0.21	0.0082± 0.0002
9 : 1 : 2	1.50± 0.30	0.0043 ±0.0004	7:3:1	1.10± 0.29	0.0058± 0.0005
8 : 2 : 0.5	1.58±0.25	0.0039 ±0.0005	7:3:2	1.20±0.29	0.0066±0.0005

**Table 2. Pharmacodynamic activity and ulcerogenicity of oral and Transdermal administration of indomethacin in arts**

Formulations	Ulcer index	percent inhibition				
		4hrs	8hrs	12hrs	18hrs	24hrs
Control (p.o.,25mg/kg) TD Patch (10 cm <sup>2</sup> )	7.86 ± 0.72	35.5 ± 4.1	30.4 ± 3.6	28.8 ± 4.9	23.8 ± 3.44	12.5 ± 7.2
F <sub>1</sub>	1.04 ± 0.31	26.4 ± 8.6	30.8 ± 9.4	38.4 ± 7.9	31.3 ± 8.4	34.6 ± 4.2
F <sub>2</sub>	1.38 ± 0.61	29.4 ± 10.5	38.2 ± 8.6	46.4 ± 10.2	50.2 ± 7.4	46.4 ± 7.6
F <sub>3</sub>	1.29 ± 0.48	38.6 ± 6.7	46.2 ± 9.2	51.4 ± 8.5	46.6 ± 6.9	50.4 ± 5.8

F<sub>1</sub> = EC : PVP : IND (9:1:2), F<sub>2</sub> = EC : PVP : IND (8:2:2) F<sub>3</sub> = EC : PVP : IND (8:2:3)  
n = 6 in each group

value was calculated. The drug content uniformity of the films was determined by UV spectrophotometric method. TLC method was followed to study the drug-carrier interactions. The X-ray diffraction studies of pure drug and various formulations were carried using Philips X-ray diffractometer (PW1140) with graphite monochromator, Cu, K<sub>α</sub> radiation (λ=1.5418Å) with chart speed 2° min and divergence slit 1°.

The *in vitro* percutaneous penetration of indomethacin through the rat abdominal skin was tested by using modified franz diffusion cells<sup>5</sup>. The excised fat-free abdominal skin was mounted on the receptor compartment facing the stratum corneum upward into the donor compartment. The transdermal patch was overlaid on the skin preparation with good contact. The receptor compartment containing 25ml of isotonic phosphate buffer (ph 7.4) containing 0.02% gentamycin as antibacterial

agent, was stirred with a magnetic stirrer and the temperature was maintained at 37 ± 1. Samples were withdrawn at regular time intervals and analyzed for drug content, after suitable dilution, using Shimadzu double beam UV spectrophotometer.

Male Wister rats weighing 120-140 gms were used for the antiinflammatory activity of the indomethacin patches against carrageenan induced rat paw oedema model<sup>6</sup> and the results thus obtained were compared with oral administration of indomethacin at a dose of 25 mg/kg. The animals were divided into five groups each containing six animals. One group served as control, to another group, suspension of indomethacin with gum acacia was administered orally and for the remaining three groups, the transdermal patches were applied. The animals were anaesthetised with urethane (1g/kg.i.p.) to restrict the movements. The polymeric film of indomethacin (10 cm<sup>2</sup>) was

applied employing a thin film of pressure sensitive adhesive. The patch was covered with aluminum foil to avoid the photosensitivity. Three hours later, Carrageenan (0.1 ml of 1% w/v) was injected into the subplantar region of the left paw. The paw volume of all the groups was determined at an intervals of 4,8,12,18, and 24h. The animals were sacrificed by cervical dislocation after pharmacodynamic studies and the stomach was excised, which were then incised along the greater curvature and the ulcers developed were examined under stereo microscope. The ulcer indices were calculated by the method of Robert *et al*.

The prepared films were smooth, uniform and flexible. The preliminary studies revealed that the drug is distributed uniformly throughout the film and no interaction between the drug and polymers used. The *in vitro* percutaneous permeation studies through the rat abdominal skin indicated that the skin flux of indomethacin was increased with increase of PVP content as well as initial drug loading dose in the film (Table 1). This is due to the fact that the PVP acted as anti-nucleating agent that leads to the inhibition of formation of crystalline drug from its solution. Thus, the improved solubility of amorphous form of the drug increase the thermodynamic activity of the drug and hence permeability. The pharmacodynamic performance of the promising film in rats exhibited good antiinflammatory activity over a period of 24 h compared to oral administration. The constant percent inhibition indicates that the drug released at a controlled rate. The ulcer indices for transdermally administered indomethacin was significantly low ( $p < 0.01$ ) compared to that after oral administration (Table 2). This is due to the avoidance of gastric mucosal contact of indomethacin by transdermal delivery.

From this study it may be concluded that the transdermal delivery of indomethacin is an alternate route of administration for prolonged action without any gastric disturbances and other side effects associated with oral administration. The pharmacokinetic evaluation of the films composed of ethyl cellulose : polyvinyl pyrrolidone : drug (8:2:2 and 8:2:3) are in progress in animal models.

#### ACKNOWLEDGEMENTS

One of the authors, P. Rama Rao thankful to the council of Scientific and Industrial Research (CSIR), New Delhi, for awarding Senior Research Fellowship. The authors are thankful to Dr. K.V. Raghavan, Director, Indian Institute of Chemical Technology (IICT), Hyderabad, for providing necessary laboratory facilities and constant encouragement. The authors also thankful to Dr. Ravi Kumar, X-ray crystallography Laboratory, IICT for XRD studies.

#### REFERENCES

1. Berner, B. and Vivian, A. J., *Clin. Pharmacokinet.* 1994, 26, 121.
2. Chien Y.W. *Transdermal controlled systemic Medication*, Marcel Dekker Inc. New York, 1987, p32.
3. Keshary, P.R., Huang, Y.C. and Chien, Y.W. *Drug Dev Ind. Pharm.*, 1985, 11, 1213.
4. Munden, B.J., Dekay, G.H and Banker, G.S., *J. Pharm. Sci.* 1964, 53, 395.
5. Keshary, P.R., and Chien, Y.W. *Drug Dev Ind. Pharm*, 1984, 10, 883.
6. Diwan, P.V., Karwande, I, Margaret. I and Satter, P.B., *Ind. J. Pharmacol*, 1989, 21, 1.
7. Robert, A., Nezamis, J.E., Lancaster C, Hancher, A. *Gastroenterol.*, 1979, 77, 433.