6.1 SUMMARY

Several technological advances have resulted in the development of different types of novel drug delivery systems, which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic effectiveness and targeting the drug delivery to a particular tissue.

In response to these advancements, transdermal drug delivery systems of several drugs have been approved by FDA and are marketed worldwide e.g.: Transderm-Scop (scopolamine) for 72 hour prophylaxis or treatment of motion induced nausea; Transderm Nitro (nitroglycerine) and Frandol tape (isosorbide dinitrate) for once a day medication of angina pectoris, Catapres-TTS (for clonidine) for a weekly therapy of hypertension, Estraderm (estradiol) for the twice a week treatment of postmenopausal syndromes and Duragesic (fentanyl) twice a week analgesic in cancer patients.

Compared to the conventional drug therapy, transdermal therapy has the potential advantages of avoiding biochemical degradation in the GIT and presystemic metabolism in the gut wall and liver, of being able to provide long periods of drug action for relatively short acting drugs, provides controlled plasma levels of potent drugs and allows administration of drugs with narrow therapeutic window.

One of the major problems in delivering a drug into or through the skin is its inherent impermeability. The primary barrier to transdermal diffusion is the stratum corneum. The tissue is composed of highly flattened keratin filled cells embedded in
a lipid / water matrix. Intercellular lipids are arranged as stacks of bilayers, which run mainly parallel to the surface of the skin.

A well known approach, which reduces the barrier function of the SC, involves the use of enhancers that can partition into and interact with skin constituents to induce a temporary, reversible increase in skin permeability.

Terpenes are receiving much attention as skin penetration enhancers due to their low skin irritancy, low systemic toxicity and good enhancing abilities. Due to these considerations turpentine oil and lemon oil were used as penetration enhancer. Penetration enhancing capabilities of NA-102 were also investigated.

Flurbiprofen, a potent nonsteroidal antiinflammatory drug, has been used extensively for the treatment of rheumatoid arthritis and its related disorders. Although it has potent pharmacological activities with oral administration, it causes unwanted problems such as systemic side effects and gastrointestinal irritation. The plasma half life after oral administration is 4-6 hours. Considering the fact that it is usually used for a longer period, it is desirable to reduce these side effects while maintaining its therapeutic blood concentration. In this context, the development of transdermal drug delivery system of flurbiprofen would provide an alternative to oral treatment and will circumvent the disadvantages associated with oral therapy.

Membrane moderated transdermal drug delivery system were developed due to the fact that they provide a steady state transdermal delivery of the drug with minimal fluctuations in plasma concentration.
The target steady state concentration of flurbiprofen was calculated using the available pharmacokinetic data ($C_{ss} = 4\mu g/ml, CI = 0.35 \text{ ml/min/kg}$). Target plasma concentration was calculated assuming the surface area of transdermal device as $9 \text{ cm}^2$ and body weight of the patient as $60 \text{ kg}$.

The maximum flux of $98 \mu g/cm^2/hr$ was obtained with 1% w/v flurbiprofen solution in solvent mixture containing 70:30 v/v of PG: IPA (30:70 %v/v). The steady state plasma concentration obtained with this permeation rate was $0.71\mu g/ml$.

Since the steady state concentration was less than the required concentration, chemical penetration enhancers viz. turpentine oil, lemon oil and NA-102 were incorporated in the optimum binary solvent mixture of IPA: PG (70:30 %v/v).

The maximum permeation rate achieved with PG: IPA (30:70 %v/v) was further increased from $98 \mu g/cm^2/hr$ to 198, 241 and 210 with the addition of 5% NA-102, 5% turpentine oil and 3% lemon oil respectively. The steady state plasma drug concentration corresponding to this was $1.42\mu g/ml$, $1.72\mu g/ml$ and $1.50\mu g/ml$ respectively. Since this steady state plasma concentration was still less than the required plasma concentration, the drug load to be incorporated in transdermal patches was increased to 100mg.

HPMC was used as a thickening agent for ease of fabrication of the reservoir type of transdermal drug delivery system.

It was found that 2% w/w HPMC resulted in desirable rheological properties with optimal transdermal permeability.
SUMMARY AND CONCLUSION

Since the maximum achieved transdermal permeation flux of flurbiprofen was still less than the required flux, the drug load of the formulation was doubled.

Three different type of reservoir transdermal delivery system of flurbiprofen were developed using PG: IPA (30: 70%v/v), 2%w/w HPMC. Containing 5% w/w Turpentine oil, 5%w/w NA-102 and 3%w/w lemon oil respectively. The reservoir solution was sandwiched between a microporous EVA membrane (3M™ Co- Tran™9702) and polyester backing films (3 M™ Scotchpak™ 9733). The vinyl acetate content of the EVA membrane was 9%.

The fabricated patch formulations were subjected to invitro skin permeation studies. The patch formulation T1 & T3 containing NA-102 and lemon oil as permeation enhancers respectively modulated the skin permeation rate through rat skin. One possible explanation could be the low vinylacetate content of the microporous membrane. It is reported that the permeation of drugs through EVA membrane increases as the vinylacetate content of the film increases.

However there was no significant effect on formulation T2 containing turpentine oil as the penetration enhancer. HPLC method of analysis of flurbiprofen in rat plasma was developed and validated for carrying out pharmacokinetic studies.

The three optimized formulations were subjected to invivo studies in albino rats. The maximum plasma concentration (C_{max}) were 17.86, 30.82 and 22.03 µg/ml respectively from formulations with NA-102, turpentine oil and lemon oil. The C_{max} of all the formulations was higher than the control formulations containing no permeation enhancer. AUC (0-α) of the formulations with NA-102, turpentine oil
and lemon oil was 1.28, 1.87 and 1.61 times higher than the control patch formulations. The relative increase in the bioavailability was found to be 2.97, 3.80, 5.56 and 4.76 times with formulations control, T-1, T-2 and T-3 respectively as compared to equal dose of orally administered flurbiprofen. Thus, the membrane moderated TD patches provided prolonged steady state concentration of flurbiprofen with minimal fluctuations and improved bioavailability.

Skin accumulation studies revealed that the considerable portion of the drug got accumulated in the excised rat skin samples to which were applied test formulations (T-1, T-2 and T-3) as compared to the formulations without permeation enhancers.

A possible explanation may be that due to the propylene glycol, increased drug partitions into the skin. However terpenes are known to cause increased lipid disruption in SC there by increasing the diffusion of the drug through the skin.

Pharmacodynamic evaluation of the formulations was carried out using rat paw edema antiinflammatory model.

The percentage swelling observed respectively at the end of 24 hours was 1.02, 1.31, 1.12 and 29.29 in formulations with NA-102, turpentine oil, lemon oil and control patch formulations containing no enhancer, respectively. The percentage swelling of 43.62% was observed in orally treated rats at the end of 24 hrs. These studies are in agreement with the pharmacokinetic studies. Due to the prolonged steady state conc. of flurbiprofen the % swelling was better controlled with the patch formulations containing penetration enhancers.
6.2 CONCLUSION

1. The aim of the study was to develop membrane moderated transdermal therapeutic system of flurbiprofen.

2. In vitro studies were performed using various solvents and their binary combinations. The maximum permeation rate was achieved with PG: IPA (30: 70%v/v).

3. The maximum permeation rate obtained with PG: IPA (30: 70%v/v) was further enhanced by 5% NA-102, 5% turpentine oil and 3% lemon oil.

4. 100mg of the drug was incorporated into transdermal patch formulations meant to release the drug over a period of 24 hours.

5. Based on invitro permeation studies three formulations, containing 2% w/w HPMC in PG: IPA (30: 70%v/v) with 5% NA-102 (T-1), turpentine oil (T-2) or 3% lemon oil (T-3) penetration enhancers, were optimized for further studies.

6. The membrane moderated transdermal drug delivery system was fabricated by encapsulating the drug reservoir in the compartment made from drug impermeable backing laminate and rate controlling membrane.

7. The EVA copolymer membrane modulated the drug release from transdermal patch formulations with lemon and NA-102 oil.

8. Histological studies revealed the superior absorption enhancing capabilities of NA-102, turpentine oil and lemon oil with negligible skin irritation.
9. HPLC method developed for the analysis of flurbiprofen in plasma samples was found to be precise, accurate and suitable.

10. The $C_{\text{max}}$ obtained in albino rats with T-1 (5% NA-102), T-2 (5% turpentine oil) and T-3 (3% lemon oil) formulations were found to be 17.86, 30.82 and 22.03 $\mu$g/ml respectively.

11. The $\text{AUC}_{(0 \text{ to } \infty)}$ of formulations T-1, T-2 and T-3 was 1.28, 1.87 and 1.61 times higher than control patch formulation containing no enhancer.

12. The transdermal drug delivery systems were found to improve the bioavailability in comparison to orally administered flurbiprofen.

13. Higher portion of drug was recovered from the excised skin samples to which were applied test patch formulations T-1, T-2 and T-3 as compared to the formulation without permeation enhancer.

14. The percentage swelling was suppressed significantly with patch formulations T-1, T-2 and T-3 as compared to the control transdermal patch formulation and orally administered flurbiprofen.

15. Further work is required to establish the utility of this system through long term pharmacokinetic studies on human subjects.
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