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Research Article

TRANSDERMAL DELIVERY OF IBUPROFEN AND ITS PRODRUGS BY PASSIVE DIFFUSION AND IONTOPHORESIS

BIJAYA GHOSH*[1], PREETHI GB[1], ROOPAK MISHRA[2], VERSHA PARCHA[2]

[1]Department of Pharmaceutics, KLE University's College of Pharmacy, Bangalore, Karnataka, India, [2]SBS (PG) institute of Biomedical Sciences and Research, Balawala, Dehradun, India. Email; bijayadd@yahoo.co.in

ABSTRACT

Oral dosage forms of ibuprofen, though popular, suffer from the limitation of gastric injuries caused by the free carboxylic group. Literature supports the development of prodrugs as well as

rate controlled delivery as promising approaches to circumvent this difficulty. The present work is undertaken to develop a series of ibuprofen esters to mask the fee carboxylic groups and to screen their potential for transdermal development.

Prodrugs were synthesized by conventional method of esterification and *in vitro* permeation studies were carried out by passive diffusion and iontophoresis at three current densities (0.5, 2.5, and 5mA/cm^2). For comparison, permeation was carried out with the parent moiety too.

Results showed in terms of passive permeability, prodrug formation was beneficial only up to the addition of one alkyl group (2,4, isobutyl phenyl ethyl propionate $P<0.05$) but thereafter permeation rate had declined. Enhanced permeability was observed in iontophoresis too but the benefit was significant ($P<0.05$) only at the higher current densities (2.5 and 5mA/cm^2).

This study suggests, of the prodrugs, 2,4, isobutyl phenyl ethyl propionate has the optimum characteristics in terms of skin permeability. Since the drug/prodrugs did not show significant benefit at the low current density iontophoresis, passive diffusion seemed to be a better strategy than iontophoresis.

Keywords: Ibuprofen, Transdermal, Iontophoresis, and Prodrug.

INTRODUCTION

Ibuprofen is a popular non-steroidal anti-inflammatory drug (NSAID) used for the treatment of musculoskeletal disorders, inflammation, fever, primary dysmenorrhoea and also in the management of mild pain. But it suffers from the limitation of gastro-intestinal (GI) toxicity and other side effects because of the presence of free carboxylic group[79]. The gastric injury allied with long term oral use of ibuprofen is caused by the combination of local irritation produced by the carboxylic group in the molecular structure and local inhibition of prostaglandin synthesis in the GI tract[2]. The utilization of prodrugs to temporarily mask the acidic group of NSAID's has been proposed as an approach to reduce or suppress the GI toxicity due to the direct contact effect and also to increase their absorption values[3, 4].

Several literatures supports prodrug approaches; Peng Wang innovatively prepared ibuprofen ligustrazinate hydrochloride, a prodrug of ibuprofen[2] and Xiangguo Zhao demonstrated glucopyranoside esters of the drug as potential prodrugs to suppress the gastric injury of ibuprofen[5]. The acrylic type polymeric prodrugs of ibuprofen (methacryloyloxy (2-hydroxy) propyl-4-isobutyl-methylphenyl acetate) had been designed and developed by Mirzaagha Babazadeh in order to minimize delivery problems and reduce GI side effects by controlling the rate, duration and site of release[6]. Apart from oral delivery, prodrug of ibuprofen has also been developed for parentral delivery. Xiuli Zhao had developed ibuprofen eugenol ester and formulated into microemulsion system for the purpose of parenteral delivery[7].

Another approach that has captured the interest of researchers is the transdermal delivery of topical anti-inflammatory agents to improve safety and efficacy of the treatment by chemically modifying the parent drug[9]. There is ample literature support for the greater advantages of transdermal approach over oral delivery and injections, which includes a non-invasive treatment regimen, bypassing of first pass metabolism and quick interruption of treatment[1,8,10]. This approach has been investigated for ibuprofen too[8]. However success of the approach is limited due to the formidable barrier provided by the skin, which is associated primarily with the outermost stratum corneum (SC) layer of the epidermis. Usually chemical enhancement technique is used to enhance the delivery of the drugs from transdermal route[11,10] but the toxicity associated with many chemical

penetration enhancers has restricted their usefulness for clinical application[12]. Hence recent innovations in transdermal research include delivery techniques like iontophoresis, which are free of the side effects of chemical enhancers. Iontophoresis enhances drug transport across the skin barrier with the assistance of an electric field, using low intensity controlled current to actively propel the drug manifold in comparison with intrinsic passive permeability[13, 14]. By nature, iontophoresis is non-invasive and reported to be free of side effects within the specific threshold of current density[15] whereas esterification represents a promising method of enhancing skin permeability of drugs by enhancing lipophilicity[17 - 18].

In present study, we have attempted to mask the free carboxylic group of ibuprofen by esterification and screened the effects of generated prodrugs on skin permeability by passive diffusion and iontophoretic technique.

METHODS

A gift sample of ibuprofen was received from Natco Industries Pvt. Ltd, Hyderabad. Esters were synthesized by standard procedure[19] and characterized by IR and NMR. Properties of drug/prodrugs are given in table 1.

IN VITRO PERMEATION STUDIES OF DRUG/PRODRUG

Passive permeation studies

In vitro passive diffusion of the prodrugs were performed using porcine ear skin. Franz diffusion cells were obtained from Neutron Scientific, Calcutta. The excised porcine skin was mounted on the donor compartment of the diffusion cells and the receiver compartments were filled with 50 ml of 0.9% normal saline. Donor compartments were loaded with 5 ml of 0.024M prodrug/drug solutions. The tops of the donor cells were covered with aluminium foils to prevent evaporation of vehicles. The temperature was maintained at 37±1^{0}C. The sample solutions were withdrawn every half an hour and concentration was measured at 264 nm using UV spectrophotometer. To compensate for the absorption of components leached out from the skin (if any) blank permeations (no drug in the donor) were also carried out. The experiments were continued for 3 hours.

Iontophoresis

Iontophoretic DC source (digital display, current 0-10 mA, voltage 0-25 V) were purchased from C-tech Psu-2510/lab Mumbai; India. Diffusion cell were fabricated by Neutron Scientific, Calcutta and silver/silver chloride electrodes were used. Donor solution (0.024M prodrug/drug) was filled in the top chambers and the bottom chambers were filled up with 0.9% NaCl. For the present study, silver/silver chloride electrode was inserted into the donor compartment whereas silver plate was inserted into anodal chamber as return electrode. Direct current (0.5mA/cm^2, 2.5mA/cm^2, 5mA/cm^2) was used throughout experiments. The receptor fluid (10ml) was withdrawn at regular intervals and replaced with fresh NaCl to maintain sink condition. The temperature was maintained at 37±1^{0}C and 3 hours diffusion study was carried out for both prodrug and drug solution

DATA ANALYSIS

Statistical analysis was performed by repeated measure ANOVA (followed by Bonferroni's test) to assess the effects of various treatments.

RESULTS AND DISCUSSION

Ibuprofen, an acidic drug with the pKa value 5.2[20] and logP 3.6[21] has low absorption and low systemic bioavilability. In oral form, the plasma concentration of ibuprofen required for effective relief of pain and inflammation in the distal areas of the body can be easily achieved. However the levels achieved from conventional dosage forms are much higher than are necessary to maintain the therapeutic benefit[22]. Many patients experience difficulty with the oral adminstration of ibuprofen related with GI distress and liver metabolism issues[23].Delivery of this drug through skin is predicted to result in greater advantages and attempts have already been undertaken to deliver ibuprofen through this route[1,24]. Several scientists are involved in controlled delivery of this drug and research is at the higher pace [5 –7,25].

Calculation based on available pharmacokinetic data shows that if the concentration is kept equal to the minimum effective concentration (10µg/ml), per hour an amount of 29.085 mg ibuprofen is eliminated from the body[26,27]. Hence for effective transdermal delivery, approximately 29 to 30 mg must be absorbed per hour through the skin. Considering the drugs poor intrinsic skin permeability this seems to be an extremely difficult task[21,28], which call for innovative strategies. In present study, we have attempted to explore two such strategies, structural modification and iontophoresis to enhance the skin permeability of ibuprofen. A series of ibuprofen esters were prepared with objective of enhancing lipophilicity. The partition coefficients of the prodrugs were given in Table 1.

Table 1: Properties of drug and prodrugs

Code	Chemical name of drug/prodrug	Molecular weight	Partition coefficient (log P)
D	2,4,Isobutyl phenyl propionic acid (Ibuprofen)	206.28	3.75
p1	2,4, Isobutyl phenyl ethyl propionate	234.33	4.35
p2	2,4, isobutyl phenyl propyl propionate	236.35	4.84
p3	2,4, isobutyl phenyl butyl propionate	250.38	5.26
p4	2,4, isobutyl phenyl pentyl propionate	276.41	5.68

It is apparent from Table 1 that prodrugs have comparatively higher molecular weights and increase in molecular weight of moieties is usually considered to affect their skin permeability in negative way. However, Waranis and Sloan[29] had postulated, the diffusivity of a series of homologous prodrugs should depend inversely on the third root of their molar volumes. According to this assumption, though esterification increased the molecular weight, flux could not have adversely affected the permeation rate, as the cubic root value of the molar volumes of prodrugs would be minimally different from that of the parent drug. According to Doh et.al[30] also, drug candidates for transdermal delivery should have molecular weight in the range of 200-500 Da. All the esters generated in this study, were well within this range (266.34 - 420.60 Da).

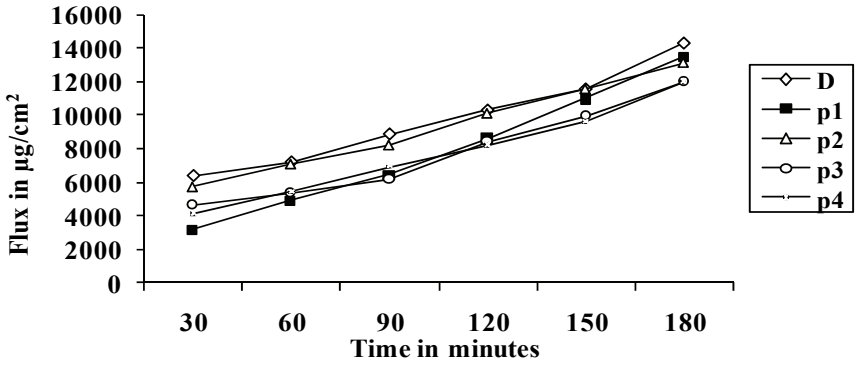
Esterification of active drugs to create prodrugs is a common practice to enhance skin permeability. Typically, once prodrug gets absorbed, they convert back into the active form of the drug into the bloodstream[2, 5, 7,31]. In percutaneous absorption, SC is considered to be the rate limiting membrane. There is a general observation, that lipophilic moieties have better solubility and partitioning into the SC, which results in enhanced skin permeation[32]. This parameter has been shown to be dependent on the drug's SC/vehicle partition co-efficient, for which octanol/water partition coefficient is often used as a surrogate[33]. It is evident from Table 1, compared to the drug, prodrugs have much higher octanol/water partition coefficient.

Permeation studies

Skin permeation studies were carried out by delivering the drug and prodrugs from a binary vehicle (ethanol and acetate buffer 20:80). Usually maximum flux can be achieved by using saturated solutions of moieties as donor as thermodynamic activity is at its maximum under this condition. However, it also imposes a practical problem of drug crystallization in patch or film[32]. Moreover, for comparison purpose activity of drugs and prodrugs in the donor medium should be equal. Below concentration level of 0.5 M, the aqueous solutions are considered to have activity comparable to their concentrations[34]. For this reason and to keep the number of permeating moieties same, the concentration of the drug and prodrugs were kept at a moderate level (0.024M). Since this concentration is much lower than the saturation value, it can be assumed that equal activity (drugs and prodrugs) had been maintained in all the experiments.

The passive permeation profile of drug and various esters are shown in the Fig.1

Fig. 1 Passive permeation profile of Ibuprofen and Prodrugs

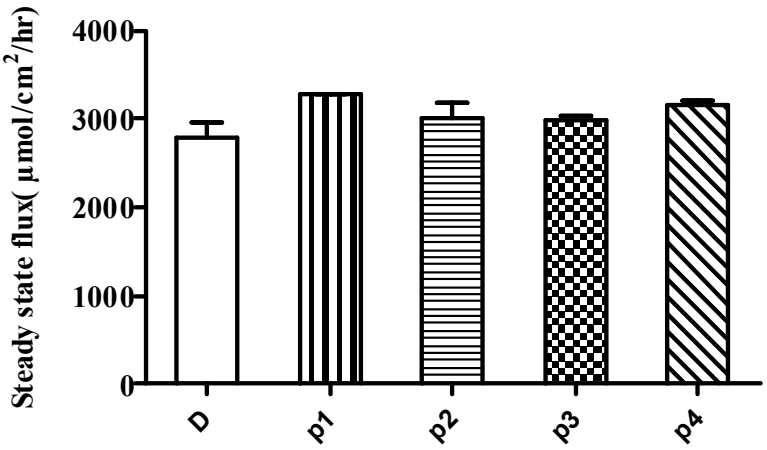


From Fig 1, it appears that the cumulative permeation of the drug and prodrugs were comparable**.** The cumulative permeation of p3 and p4 were even lower than the parent drug.

From Table 1 it can be seen that these two prodrugs p3 and p4 has got the highest lipophilicity, yet their permeation rate was lesser than the prodrugs of lower lipophilicity. This can be explained from the fact that a high value of octanol/water coefficient may favor the delivery of a moiety into the SC, but not necessarily favor its diffusion into the more hydrophilic regions of epidermis and dermis.

In a series of drug derivatives, permeation rate often reaches a limiting value with a compound of intermediate lipophilicity. Compounds with very high lipophilicity may not be highly acceptable the viable skin[35, 36] and reservoir effect into the SC may contribute to this factor[32]. The steady state flux (SSF) of drug and prodrugs are shown in Fig 2.

Fig:2 Steady state flux of Ibuprofen and Prodrugs in passive permeation



It is apparent that SSF of all prodrugs was higher than that of drug. However, when data were statistically analyzed only p1 showed significant increase ($P<0.05$) in SSF over that of the drug. For other prodrugs, the enhancement of SSF was not statistically significant ($P>0.05$). Clearly the addition of the first CH_2 group increased the skin permeability but further addition of CH_2 made the molecules too lipophilic to permeate through the hydrophilic dermal layer. To pass through the hydrophilic layer of skin, a moiety should have some hydrophilicity too. It is possible that the advantage of high partition coefficient might have been counteracted by the reduction of hydrophilicity in the prodrugs.

Number of studies has suggested that iontophoresis of prodrugs result in enhancement of transdermal permeation[37,38]. Hence the drug and prodrugs were subjected to iontophoresis.

Fig 3, 4 and 5 depict the iontophoretic profiles of drug and esters at different current densities. It appears that at all current densities (Figs. 3,4,5) p1 showed the highest cumulative permeation but the enhancement was found to be statically non significant.

Fig. 3 Iontophoresis of Ibuprofen and Prodrugs at 0.5mA/cm^2

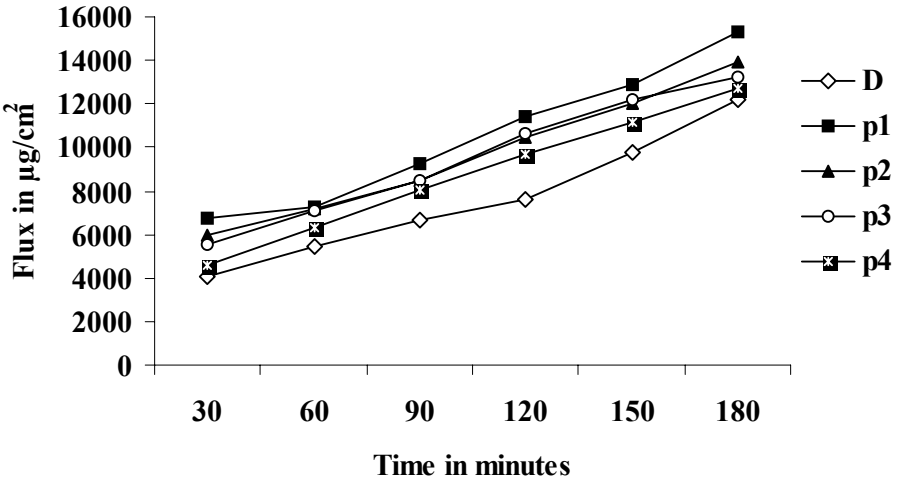


Fig. 4 Iontophoresis of Ibuprofen and Prodrugs at 2.5mA/cm^2

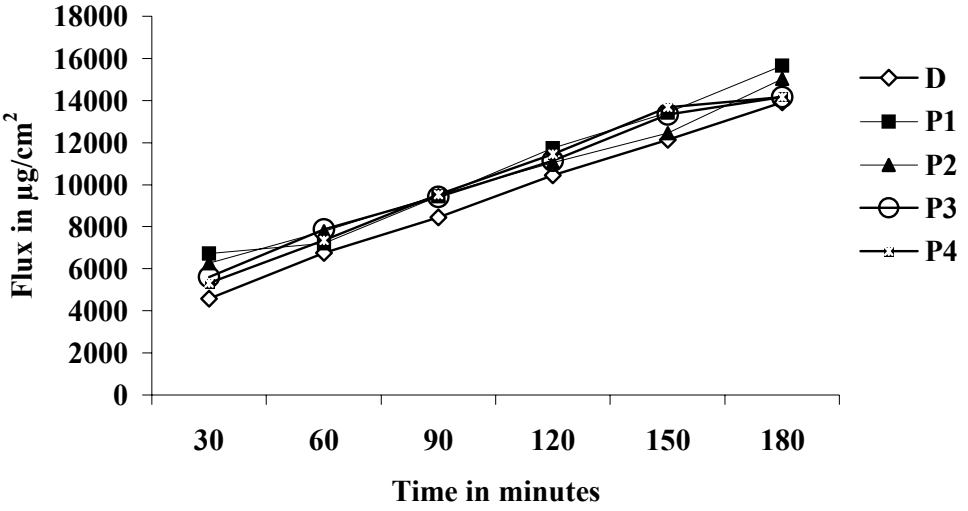


Fig. 5 Iontophoresis of Ibuprofen and Prodrugs at 5mA/cm^2

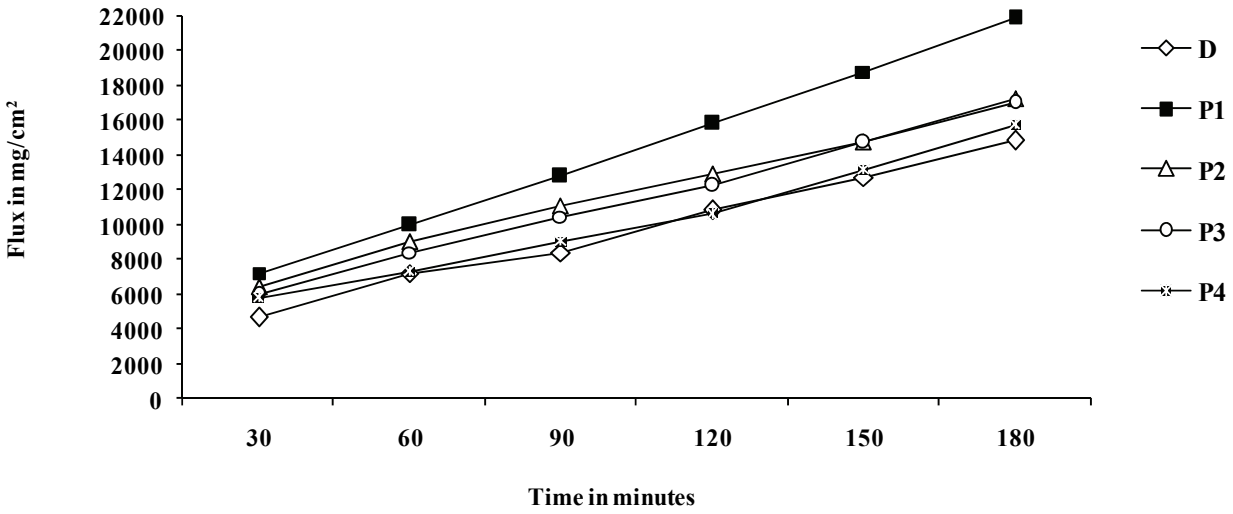
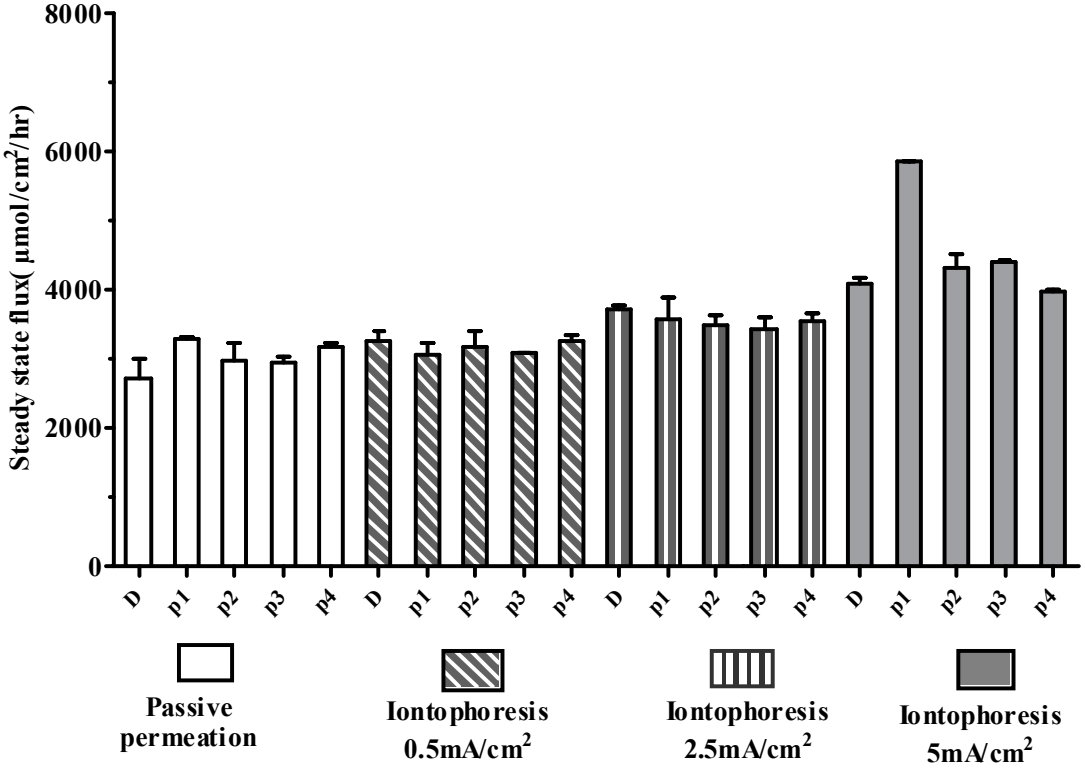


Fig .6 Steady state flux of Ibuprofen and Prodrugs in Passive permeation and Iontophoresis(0.5, 2.5 & 5mA/cm^2)



Under the influence of electrical force, a number of permeation process undergo simultaneously. The flux obtained under such process is the sum total of the electrorepulsive, electroosmotic and passive contributions[39] Electroosmotic flow occurs when voltage difference is imposed across a charged membrane. Since the human skin are negatively charged above the pH 4 and counter ions are positive, direction of the electoosmotic flow is from anode to cathode[40]. Hence the permeation of neutral moieties like esters is benefited from anodic delivery. The observed increase in SSF at higher current densities might have resulted from this electroosmotic contribution. But the current densities above 0.5mA/cm^2 considered unsafe and hence passive permeation rather than iontophoresis seems to be the more practical approach for transdermal ibuprofen delivery.

CONCLUSION

The experimental results suggest, of the prodrugs only 2,4, isobutyl phenyl ethyl propionate (p1) showed significant flux enhancement in case of passive diffusion. In low density (0.5mA/cm2) iontophoresis though there is apparent increase in cumulative permeation, the flux enhancement was not statistically significant. However significant enhancement of SSF ($P<0.05$) was observed when current intensity was increased (2.5 and 5mA/cm^2), the process cannot be justified in terms of risk benefit ratio. Numerous studies have reported that 0.5mA/cm^2 is physiologically tolerable current limit[37,18]. Hence passive diffusion rather than iontophoresis should be the preferred mode of transdermal delivery for the ibuprofen prodrugs

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