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The effects of fibers on transdermal delivery of ketoprofen from a hydrogel containing ion exchange fibers

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1. INTRODUCTION

Ketoprofen(2-(3-benzoylphenyl)) propionic acid , KP, is a non-steroidal anti-inflammatory, analgesic and antipyretic drug[1,2,3]. Athough KP has a potent inflammatory action, it has undesirable side effects on the stomach gastrointestinal complaints after oral admiration like other NSAIDs[4,5].Therefore, many efforts made to avoid the oral side effects have been carrying on. With no doubt, topical administration is one of the best ways to overcome the difficulty and to provide higher concentration at the target compartment[6] leading to higher efficacy.

There is a great interest to develop new transdermal devices, which can control and sustain the delivery of drugs. When the device controls the transdermal drug flux other than the skin, whose permeability changes with age and anatomical site[7], the rate of drug into the blood stream is more predicatable and reproducible. Ion-exchange materials have been studied as vehicles in transdermal drug delivery system these days[8,9,10]. Changed drugs are bound into the ion-exchange groups of the fiber until they are released by mobile ions, so that it provide a promising way to achieve controlled drug release and also enchance drug stability[11].

This paper first reports the results of investigations in novel ion exchange fibers which were incorporated into the hydrogel vehicle of a transdermal system. The objective of this work were: (1) to determine the in vitro transdermal permeation profiles of KP across rat skin and Visking membrane from the complex vehicles (2) to study the role of fibers play during KP the transport from the composite vehicles (3) to investigate in vitro iontophoretic assisted drug delivery from the complex through rat skin compared to passive transdermal system;

2. MATERIALS AND METHODS

2.1 chemicals

Ketoprofen was the model drug studied from the Southwest synthesised drugs manufacture joint-stock company (China), Carbopol 940 of molecular weight 4 000 000 was supplied by NoveonTM (The specialty Chemicals Innovator) . All the other chemicals were at least analytical grade and were used without further purification. Deionized water with a resistivity of 18MΩ/cm or greater was used to prepare all the solutions. The pH was adjusted by the addition of chlorhydric acid or sodium hydroxide (0.1 or 1.0M).Sliver and silver chloride (purity ＞99.99％) were obtained from Green Tree Scientific ＆ Instrument Co.

The ion-exchange fibers studied was strong anion-exchanger ZB-2, Poly (propylene-g-vinylbenzyltrimethyl-ammonium-chloride) .The fibers were used in staple form(170μm×30μm),and the maximum ion-exchange capacity was about 3.0 mmol/g of fibers. The ion-exchange fibers were obtained from Guilin Zhenghan Co. ltd (Guangxi, China).

2.2 Preparation of rat skin

Male rats of about 250 g obtained form Shenyang Pharmaceutical University were sacrificed by excessive ether anesthesia. After the removal of hair skins using an animal hair clipper, the skins were harvested from the abdominal part of the rats. Then the residual subcutaneous fat adhering on the dermis side was wiped by using scalpel and isopropyl alcohol. Finally, skin was washed in water and subsequently in PBS pH 7.4, and packed in aluminum foil and stored in refrigerator at –20℃.

2.3 iontophoretic apparatus

ThepowersupplysystemwasmadebyRuoyacompany（Beijing，China）, which was used to provide a constant direct current. During the experiments, one pair of the drive electrodes, made from a silver plate (anode) and a silver wire coated with silver chloride（cathode）, were separated from the donor and receptor chambers by salt bridges.

2.4 preparation of the vehicles

The strong ZB-2 anion-exchanger (100 mg of staple fibers) was bundled up inside a porous membrane. The mobile counter-ions initially attached to the trimethylammonium groups were chloride ions. The fiber bundles were hydrated for 1 h with deionized water and were activated for 8 h in 1% NaOH solution before experiments. Thereafter, to remove the excess alkali, the fibers were washed with deionized water until the pH was about 8.The fibers were immersed in a 0.5% (w/v) KP solution over night (50mg of loading solution/10 mg of the fibers), first for 4 h and then transferred into a fresh loading solution for 12 h. The pH of the KP solution was adjusted to 8 with 1M sodium hydroxide. At this pH both the KP and the fibers remained in a ionized form. Then the fibers were washed with a known amount of water and squeezed dry at room temperature and subsequently at 313 K in an oven to constant weight. The amount of adsorbed drug in the fibers was determined by HPLC from the different concentration in the collected washing solutions and the initial solution.

Carbopol gel base formulation and preparation is as follows: CP 1.0g, NaOH 0.4g, ethanol 40ml, sodium metabisulfide 0.1g,water qs to 50ml. CP 940 was dispersed in two-third of the water overnight. Ethanol and some other materials (SOM) were added to this solution for stirring 4h at room temperature. The NaOH was dissolved in the remaining water and was added to the polymer dispersion, and then was stirred with continous agitation about 8 h. The pH of the products were about 7. The composite vehicles prepared marked by simple gel, KP+fibers gel and KP-fibers gel with the different representatives of SOM, which substitute for KP, a physical mixture of KP and fibers, and KP-loaded fibers.

2.5 Permeation studies

Specially designed vertical-type glass diffusion cells with side-arm were used. The available diffusion area was 2.25 cm2 and the volume of receptor compartment was 13ml. The rat skin or Visking used were hydrated for 2 h in PBS pH 7.4 prior to mounting in the cells with the dermal sides of the skin facing the acceptor compartment The transport of KP from the vehicles (0.4g) was studied across the rat skin, some experiments were also carried out across Visking. A transdermal disc was placed on the the receptor medium used was phosphate-buffered saline (0.05 M; pH 7.4) at 37±1℃. It was stirred magnetically at 300 rpm. Samples were withdrawn at 1, 2, 3, 4, 6 and 8 h intervals and replaced with PBS pH 7.4.

As to the electrically assisted transport, the procedure was similar to passive transport described above, with the skin placed between the anodal and the acceptor compartment. The cathodal side was approximately 3 cm below the rat skin in the receptor compartment filled with PBS pH

7.4. A direct current was 1.2 mA and the impulse frequency was 2000Hz. The voltage was adjusted to maintain a constant current value. A constant current of 0.5 mA/cm2 was applied for 4 hour, and for the next 4h, the passive flux was monitored.

2.6 Analyical method

Collected samples during the experiments were injected into the HPLC system and analyzed by UV detector (Jasco, Japan). According to the previous paper [12], analyses were performed on 5µm C18 (20×4 mm id.)Column (Sigma Aldrich) . The mobile was adjusted to a mixture of acetonitrile and phosphate buffer 0.02 M pH 3.5 (40:60,v/v). The selected and optimized conditions were as follows: injection volume 20 µl, the mobile phase isocratically pumped at a flow rate 1.0 ml·min-1 at ambient temperature and the detection wavelength 233nm. In this condition the retention time of KP was 6.60 min. The concentration of KP was calculated by comparison with a linear calibration curve which was determined using reference standard solutions and each experiments studied at least in triplate.

3. RESULTS AND DISCUSSION

3.1 effect of fibers during permeation

Besides for the rat skin, the Visking was used in passive transport without any real hindrance during diffusions. The membrane was treated the same as rat skin described above. The simple gel and the KP-fibers gel complex were used in this experiment. To assess the difference made by the fibers in the formulations, the two compositions were placed on the Visking and the KP diffuse passively across the membrane into PBS pH 7.4 (0.05 M) medium.

To assume the fraction rate control provided by factor named A, the effect of influencing factors can be determined using the date from release tests as following equations:

Fraction control by factor of

$$A\ (FA,N) = \frac{T,t}{A,t} \quad (1)$$

Where A,t is the dose delivered into and across the membrane during the intended application period ,and T, t is the amount of drug released into an aqueous sink without the interference of the factor A. FA,N in this paper is the inhibitor effect of factors.

Table 1 Rate control of KP delivered from the formulations

Number	Formulation	condition	A,8 (µg·cm-2)	T,8 (µg·cm-2)	FA
1	KP gel	AcrossVisking	202.64	304.17	1.50
2	KP-fibers gel	Across visking	75.36	269.81	3.58
3	KP-fibers gel	Across rat skin	45.91	269.81	5.87

A,8: KP release into the receptor medium ;T,8: the amount of KP released into a mixture of PBS p H 7.4 and 1 M CaCl2 solution ,as to breaking the structure of gel;

FA : different means following the number 1, 2 and 3, means the fraction control by the gel ,the fraction control by the aggregate effects of gel and fibers, and the fraction control by the summation of effects of gel ,fibers and skin respectively.

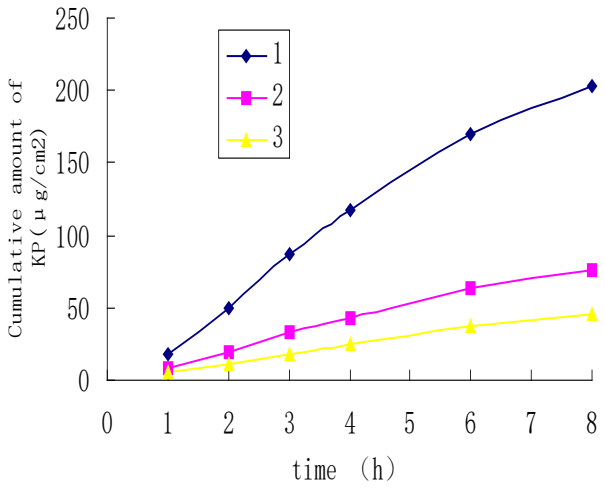

Fig.1

Permeation profiles of KP from different formulations with different conditions, the content of KP in the formulations is 1.4 mg/ml.

3.2 effect of KP concentration

The effects of drug concentration on its release from simple gel was studied according to KP concentration of 1.4 and 7.0 mg/ml. The release rates of KP from the simple gel of different drug loading dose were studied across rat skin. The release of KP from the simple gel with higher concentration showed higher rate of release. However, there was not a good correlation between the concentration of KP and release rate (fig. 2), with the longer time the higher multiple of release rate. So it could concluded that the gel could not control the KP release from the formulation and pass through the skin predictively.

Furthermore, the fibers in the formulations investigated was to decrease its rate of release when compared to the simple gel at the same level of KP, especially at the higher level of KP concentration (fig .2, and fig. 4 (A)).

It couldn't be considered as a solubility limitation of KP in the receptor medium, because the solubility of KP in the PBS pH 7.4 was found to be 1241mg/100ml at 37°C. It could be explained by the strong interaction between KP, Carbopol 940 and the fibers ZB-2, such as hydrogen bond formation, electrostatic interaction or physical (hydrophobic) interactions. The Carbomers contain between 98.7% and 99.9% acrylic acid with a neutralization of 75% normally occurring at pH 7.0[13], which was of negative electricity at pH 7.4.The pKa of fibers was about 8, which was of positive electricity partly during the release condition (pH 7.4). The KP (pKa 4.7) was negatively charged at pH 7.4. KP is held tightly with

the fibers with the hydrophobic and weak electrostatic interaction until the formulation was placed to transport to the receptor medium (pH 7.4) in the permeation studies, the interaction turned to hydrogen bond formation and strong electrostatic interaction, and the CP competed with the KP interacting with fibers .This interaction between the KP and fibers became stronger for higher concentrations, so the fibers played critical role in the controlling release of KP.

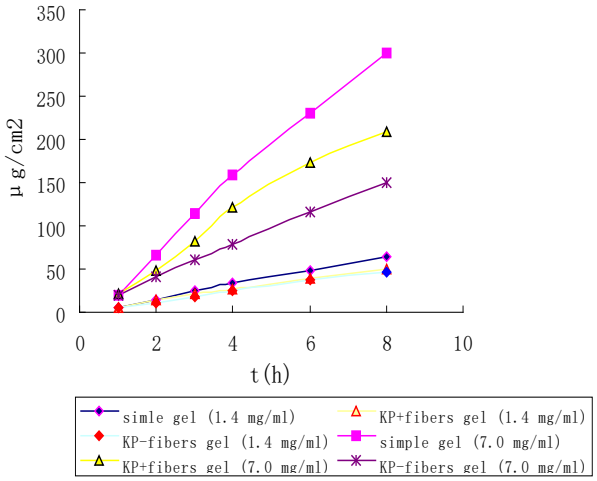

Fig. 2
The release profiles of KP into PBS pH 7.4 (0.05 M) from the vehicles made by different ways. Different concentration of the KP in the vehicles was 1.4 mg/ml and 7.0 mg/ml , and the release rates were measured across rat skin.

3.3 effect of prepared ways

Ion change fiber-gel discs could be prepared in two ways. In this paper, the formulations (marked by KP-fibers gel) prepared had been prescribed above (2.4 preparation of the vehicles) . In order to simply the procedure of discs, exploratory work was made .The second way (marked by KP+fibers gel)was as follows: the fibers was added to a 2% CP gel mix to which KP at the required concentration had been added already. The vehicles prepared in two ways shows the necessity of the step of preparing KP-fibers. It was also shown that the quantity of fibers and KP could affect these delivery rates.

It was shown contrasting profiles of KP across the rat skin from the vehicles by different procedure (fig.3). The corresponding overall concentration of KP in these vehicles were 1.4 and 7.0 mg/ml, respectively. The KP release rates across skin were seen to be similar with low concentration (1.4 mg/ml) from the both vehicles made by different ways, however, there was completely different phenomenon when the KP at higher concentration (7.0 mg/ml). These differences are probably attributable to differential affinities of fibers to KP for the complex matrices. Earlier work had shown that the combinations of fibers and gel control the KP delivery. The gel had principal contribution to the rate of release with the lower quality fibers in the formulations, and the ion exchange action could take place between fibers and the KP within spacious bulk during proceduring vehicles partly, so the role of the fibers played was unobvious. When the formulations were amplified, the effective of fibers that hindering movement within the fibers action of electrostatic interaction with KP. Moreover, comparing the profiles in fig.2, the higher concentration KP in the formulation the higher restrained rate controlled.

3.4 the electrically assisted transport

The cumulative amount of release versus time profile of the KP iontophoretic transport across rat skin in Fig. 3 and Fig. 4 demonstrated an enhancement on releasing process. The faster response of KP transport was obvious during iontophoretic period and the post passive transport, so the real steady state achieved was advancing to the paralleling passive transport. Meanwhile, the flux increased dramatically with the electrically assisted action. However, the flux of the simple gel was about 2-fold increase and the formulation of KP+fibers gel or KP-fibers gel was about 4 folded increased. It could be explained that the vehicles containing fibers could be of interaction with free ions. According to the Eq.1 proposed by Phipps and Gyory[14], the higher the level of ion competition the smaller the chance for the drug carrying the charge, which decreased the competition between the free ion to the drug ion to carry the current .

$$J_d = \frac{t_d I}{Z_d} \quad (2)$$

In which Jd,td and Zd are the flux, the transport number and the valence of the drug, I is the current density and F is the Faraday constant.

Simultaneously, the drug transport number increased owing to the concentration of the drug increased according to Eq. (2), which supported by the date from fig.4 and fig. 5(B). However, an electrically driven flow of ions across a membrane having a net charge can induce a coupled flow of solvent called electroosmosis[15]. The relative decrease in flux values corresponding the release from the formulations including fibers could be understood by the electro-osmosis action, which is also increasing with the higher flux of KP ions. Without the hindering of fibers, the electro-osmosis effect plays a more significant role during the electrically assisted transport, which could support the lower level increased flux results of simple gel (about 2-fold) ,comparing with the vehicles containing fibers (about 4-fold)(Fig.5).

Meanwhile, it is possible that at higher drug concentrations, the transport may become independent of preparing way, probably because of the decreasing ionic bond between KP and fibers in the complex gel by the electrically driven force. In other words, it implies that the processing of preparing complex vehicles could by either of the two ways, so the preparation could be simplied by the second way when using electrically driven power. Furthermore, the fibers in the matrix increase the electroconductivity as the approximate by the on-exhchange function part.

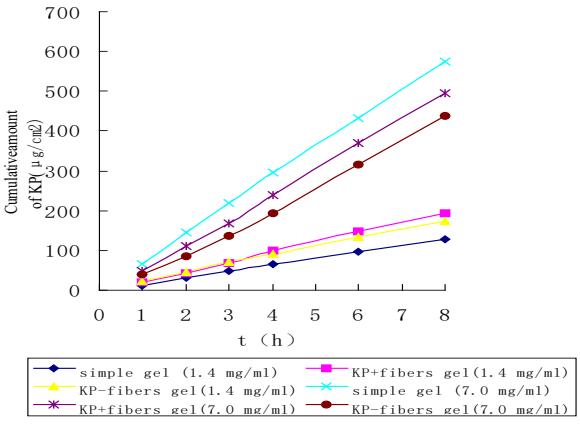

Fig.3 the cumulative amount of KP electrically assisted versus time of 1.4 mg/ml and 7.0 mg/ml in the presence of 0.05 M PBS p H 7.4. The current was on during the first 4 h and off during the last 4 h.

3.5 Release kinetics

Stead-state flux (JS) was calculated based on the Fick's law of diffusion

[16]. The term estimated was given,based on the date gained by the profiles of delivery, the real steady-state situation was after 4 h. For this reason the JS was calculated from the slope of the plot between 4 and 8 h. Fig. 4 also illustrates the response of the KP concentration to changes in drug delivery increased amount of KP delivered by increasing 5-fold concertration in the vehicle. Calculations were done using the approximate model, the Fick' model[17]. This model was used to predict the changes in the fractional release profile, predicting that the an 5-fold increased. However, the date showed that just about 3-fold increased during passive delivery and 4-fold with the electrically assisted. The reason for the discrepancy was the assumption of the Fick's model or the various quality of the rat skins. Meanwhile , there were much less increasing effects on the vehicles containing fibers according the fig. 4, illustrating the fibers acted as a soft-buffer agents in the formulations. Both values showed on the profiles (fig. 4) due to the rate limiting added by the fibers, large changes in the drug concentration have little impact on skin flux.

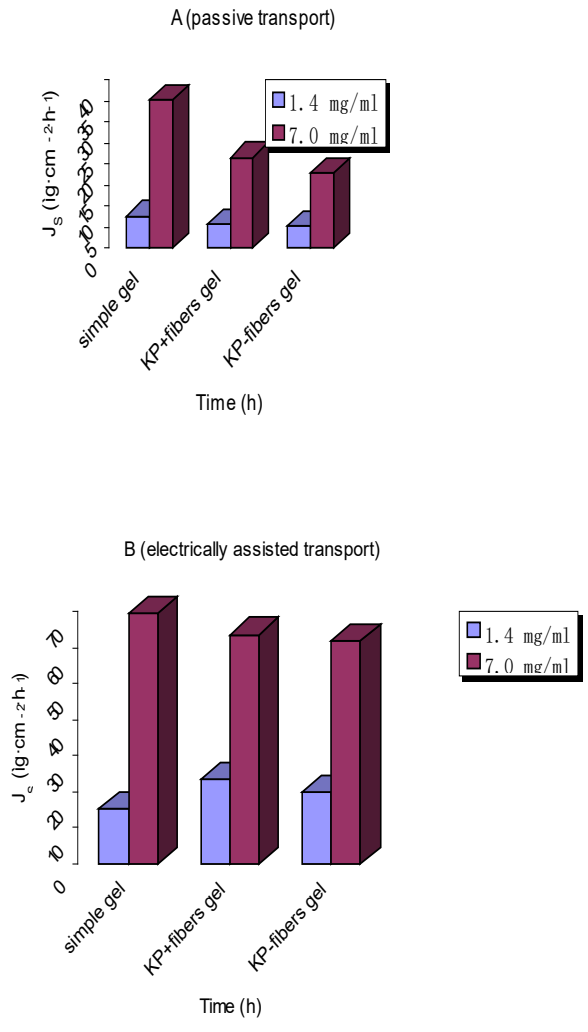

fig.4 (A) Flux versus time profile of the passive transport across rat skin of 1.4 mg/ml and 7.0 mg/ml in the presence of 0.05 PBS pH 7.4. (B) electrically assisted transport on the same conditions as passive transport There were several Mathematical modeling of transdermal drug-delivery systems. For example, the layer controlled model was described by Fickian diffusion equations and the matrix diffusion controlled model governed by Higuchi's law of diffusion, though there are several assumptions were made ideally in the models[18]. The two models were used to simulated the cumulative amount of release profiles in this paper (Fig .5). The fraction of the cumulative amount of release, flux, transport at time t, assuming a linear with the flux and t or t1/2, a comparison of the correlation coefficient in predicting the model which is agreed closely. From the the correlation coefficient comparison (in order to enlarge the discrepancy, replaced by R2) by fig.5, it was seen that the Higuchi's equation satisfied for the the drug release from the simple gel, and changed a little to Fick's equation with the fibers in the vehicle. This findings implied that the fibers act as another layer similar to the fibers limiting the transdermal delivery, supported by the previous findings (3.1 effect of fibers during permeation).

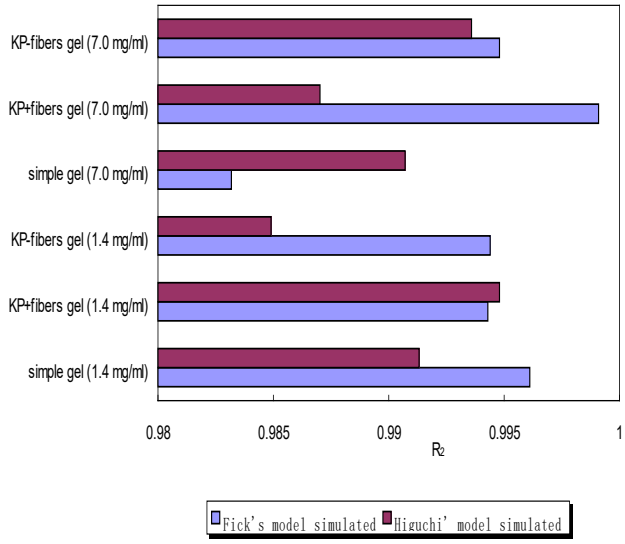

Fig. 5 the correlation coefficient comparisons simulated by different models according to the cumulative amount of KP release from different formulations across rat skin were plotted as a function of time.

The experimental data measured when the compounds were allowed to permeate the rat skin with electrical assistance was shown in Fig.3 where the relationship between the cumulative amount of the drug release and the time was seen to be linear, conforming to the Fick's model. The quantitative parameters of calibration graphs were in Table 2. The Higuchi model was used in the hydrogel containing ion exchange resins prescribed by O.M. Conaghey and J. Corish (1998)[19]In order to simplified the parameters for the passive diffusion (Table 3), the Higuchi's model adopted, simulated to which the correlation coefficient was almost more than 0.99 .

Table 2
Parameters obtained when release data were analysed on the basis of control by matrix diffusion through the vehicle (Higuchi's equation) with the passive transport, number of standards 5.

Concentration (mg/ml)	pattern	Slope×102 (mg·ml-1·t1/2)	Lag time (min)	Correlation factor
1.4	simple gel	3.275±0.90	0.94	0.996
	KP+fibers gel	2.448±0.13	0.84	0.997
	KP-fibers gel	2.287±0.05	0.87	0.992
7.0	simple gel	10.766±0.46	0.89	0.995
	KP+fibers gel	7.178±1.13	0.82	0.993
	KP-fibers gel	15.509±0.22	0.95	0.997

Table 3
Parameters obtained when release data were analysed on the basis of control by layer pemeation through the vehicle(Fick's equation) with the electrically assisted transport, number of standards 5.

Concentration (mg/ml)	pattern	Slope×102 (mg·ml-1·t1/2)	Lag time (min)	Correlation factor
1.4	simple gel	1.630±0.74	0.07	0.998
	KP+fibers gel	2.512±0.82	0.20	0.998
	KP-fibers gel	2.132±0.11	0.20	0.996
7.0	simple gel	7.261±0.38	0.02	0.997
	KP+fibers gel	6.435±0.67	0.29	0.996
	KP-fibers gel	5.770±0.27	0.50	0.998

Conclutions

In conclusion, this study has shown that KP can be delivered at a constant dose transdermally from vehicles containing fibers, which can control the the release rate of drug decreasing the effect of concentration varied.

The polymer matrix of microporous membrane was impermeable to the drug , and the capillary system generated by the circular cylinder fibers, which is similar to the capillary system in the skin represented sink conditions.

The use of iontophoresis to facilitate underlying deep tissue penetration of drugs [20]after topical application will be most beneficial in the treatment of osteoarthritis, soft-tissue rheumatism and other deep rooted local inflammatory conditions associated with sports injuries .Iontophoresis significantly enhanced transdermal delivery of the simple gel , the KP-fibers gel or KP + fibers gel, as compared with passive transport. The in vitro results suggest that a better release profile achieved by iontophoresis with rapid onset of action. The results , however, needs to be tested with different physicochemical properties, and in vitro studies will be required to support in vivo conclusions and develop in vitro–in vivo correlations. These studies suggested that iontophoretic delivery maybe independent of the type of skin studied ,although factors such as nature of the skin (normal vs diseased) and site of application still need to be evaluated.

The concentration profiles derived may be used to better understand the process and to assess the impact of fibers on the delivery rate. An understanding of drug permeation through the vehicle and the skin is also anticipated, allowing for the development of more accurate, controlled delivery of active ingredients. These studies, though limited, may lead to suggestion that ,by iontophoretic delivery iontophoretic delivery or using enhancer, which is need to be studied later, it should be possible to increase the diffusivity of the skin, so that the fibers becomes more significant effective in controlling transdermal delivery and to replace the role of skin limiting step, which could be independent of the type of skin studied ,although factors such as nature of the skin (normal vs diseased) and site of application still need to be evaluated.

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