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Comparative evaluation of ion exchange resins and fibers in iontophoretic transdermal delivery of sumatriptan succinate

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ABSTRACT

Iontophoresis is a convenient and suitable technique for delivering charged sumatriptan succinate (SS) across the skin. The objective of study was to examine the applicability of ion exchange resins and fibers as drug carrier to enhance the efficiency of transdermal iontophoresis. The complexes of drug with cationic resins Indion 204 and Indion 224 (DRC-1, DRC-2) as well as with fibers Smopex 102 and Smopex 101 (DFC-1, DFC-2) were formed by batch method. These complexes were characterized by DSC and PXRD and compared for drug loading, drug release and permeation across rat skin. Effects of constant and pulsed current iontophoresis on drug permeation were also evaluated. The iontophoresis study was conducted using silver–silver chloride electrodes across rat skin. The results suggested that fibers due to their open structure showed more drug loading and release compared to resins. The transdermal flux as well as amount of drug permeated from drug-fiber complexes was higher as compared to that of drug-resin complexes and drug solution. DFC-2 assisted with pulsed iontophoresis at 50 % duty cycle significantly increased the skin permeation of SS and reduced the fluctuation in drug permeation with constant drug delivery compared with the passive controls. Copyright © 2016 VBRI Press.

Keywords: Iontophoresis; ion exchange resins; ion exchange fibers; sumatriptan succinate; transdermal drug delivery.

Introduction

Migraine is a common and disabling neurological disorder characterized by increased brain sensitivity or hyper excitability and recurrent headaches manifesting in attacks lasting 4 to 72 h. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea, photophobia and phonophobia **[1, 2].** There are numerous formulations of drugs designed for the treatment of migraines. Among the most active ingredients available in such anti-migraine compositions are 'Triptans' **[3]**. This therapeutic group includes sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan.

Sumatriptan a potent and selective serotonin receptor agonist at vascular receptors of subtype $5HT_{1B/1D}$ is the most frequently prescribed drug in migraine therapy **[4]**. It is available in oral, nasal, and injectable formulations, and recently as a transdermal delivery system (Zecuity). The bioavailabilities of this drug, when administered intranasally, orally and by subcutaneous injection, are approximately 15, 14, and 96 %, respectively **[5]**. Low bioavailability after intranasal and inconvenience associated with subcutaneous injection, administration through these routes is a least attractive option for patients. One of the primary issues with oral sumatriptan is nausea and vomiting associated with a migraine episode and the low bioavailability due to presystemic metabolism and incomplete absorption. Moreover sumatriptan has short half-life (2.5h), hence frequent administration is needed. These limitations associated with current sumatriptan formulations (i.e. oral, nasal, subcutaneous) result in delaying or avoiding treatment by patients [**6]**. Transdermal delivery is an alternative to these methods. It is well-established route of administration with benefits including avoidance of the gastrointestinal tract and first pass metabolism, sustained and controlled delivery and convenient administration **[7, 8]**. Weakly lipophilic sumatriptan (log $K_{o/w}$ =0.93) has poor permeation profile across skin and thus it is unlikely that passive diffusion could deliver therapeutic amount of drug **[9]**.

Iontophoresis is one of the most promising techniques for enhancing skin penetration of drugs. It is a facilitated movement of ions across a membrane under the influence of an externally applied small electrical potential difference (< 10 V). Current density up to 0.5mA/cm^{2}is considered safe for patients **[10]**.Since the drug delivery is proportional to applied current, significant advantages of iontophoresis include the possibility of preprogramming the drug delivery, dose tailoring on an individual basis, or time tailoring in a constant or pulsatile fashion **[11]**. The

continuous application of direct current iontophoresis can result in the polarization of the skin that may operate against the applied electrical field and reduce the magnitude of effective current carried across the skin **[12]**.The buildup of this polarizable current can be overcome by using pulsed direct current that is delivered periodically **[13]**.'Off period' of the pulse allows the skin to depolarize and discharge the current from the skin, leading into a state that no residual charges remain in the skin by the start of the new pulse **[14]**. Iontophoresis is a convenient and rapid method of delivering water soluble, ionized medication into the skin. Therefore the transdermal iontophoresis will be suitable for delivering polar and charged sumatriptan across the skin.

Ion exchangers are class of functional materials having fixed ionic sites bonded to their framework held together by chemical bonds. Ion exchange materials are available in different forms and structures depending on origin, physical form (morphology), immobilized functional group, and their functions. The strength of interactions (formed between the mobile counter-ions and the fixed ionic groups) and thus the drug loading/release depend on the morphology of the ion exchange material and chemical nature of the functional groups (e.g. $–SO_3H$, –COOH). Ion exchange materials are available in various morphologies like resins and fibers. Ion exchange resins have cross-linked grafted side-chains whereas fibers are non-cross-linked polymeric structures. Ion exchange groups of resin are located within the spherical bead. Unlike resins, the ion-exchange groups of fibers are located on the surface which enables an easier access to the exchangeable counter ions and fixed ionic groups on the material. The ion-exchange process is more rapid and efficient in the case of fibers due to smaller shell thickness and larger surface area to unit volume ratio **[15].** The schematic representation of ion exchange resins and fibers is shown in **Fig. 1**.

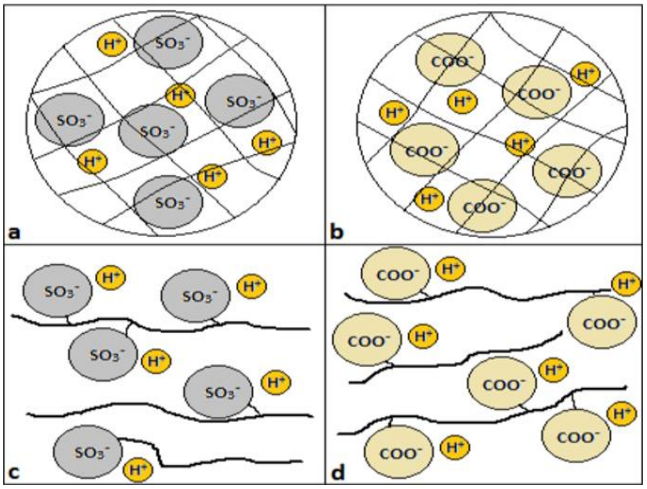

Fig. 1. Schematic representation of (a) resin beads with $–SO_3H$ functional groups, (b) resin beads with –COOH functional groups. (c) fibers with $–SO_3H$ functional groups, (d) fibers with –COOH functional groups.

The interest in the use of ion-exchange material along with iontophoresis is to create a stable drug reservoir, to provide a controlled and constant drug delivery and to improve the efficiency of iontophoresis **[16]**. The main reason for low efficiency of the iontophoretic drug delivery is that the fraction of the total current contributed by the drug ions is very small. Ionic drugs usually contain metal ions or acid radical ions, and these small ions' conductivity is much stronger than that of the drug ions, so their presence reduces the efficiency of transmission of the drug by iontophoresis. Ion exchange material improves drug's iontophoresis efficiency by inhibiting the migration rate of these small competing ions present in the system **[17]**. In the present work, four ion exchange materials i.e. I-204 (resin with –COOH group), I-224 (resin with $–SO_3H$ group), S-102 (fiber with –COOH group) and S-101 (fiber with $-SO_3H$group) were selected.

Transdermal permeation of ionic drug (SS) can be facilitated by the application of iontophoretic technique **[18, 19]**. The current literature till date does not reveal any study for investigation of iontophoretic transport of SS from drug loaded ion-exchange material as resins or fibers. The important considerations which justify the incorporation of SS in transdermal therapeutic system are nausea and vomiting associated with a migraine episode; incomplete absorption and presystemic metabolism; low oral bioavailability (~15 %) and short half-life (2.5 hrs).Transdermal iontophoresis would improve the penetration of polar and charged SS across the skin by reversibly altering barrier properties of skin. In this study it was hypothesized that ion exchange materials with iontophoresis improve the permeability of SS across skin as well as adds the benefit of controlled, predictable drug delivery. Therefore the main objective of the study was to examine the effectiveness of ion exchange resins and fibers as drug carrier material to enhance the efficiency of transdermal iontophoresis of SS. To achieve this objective, the work was divided under these headings:(1) to determine percent drug loading on ion exchange material (2) to determine the in vitro release profile of SS across 0.22 µm microporous membrane from the ion exchange material (3) to investigate the in vitro transdermal delivery of SS with assistance of continuous direct current and pulsed current iontophoresis from the system across rat skin compared to passive transdermal system.

Experimental

Materials

SS (Mylan laboratories, Nashik, India) was obtained as gift sample. Ion exchange resins Indion 224 ($-SO_3H$ group, I-224) and Indion 204 (-COOH group, I-204) were obtained from Ion Exchange India limited, Mumbai, while ion exchange fibers Smopex-101 ($-SO_3H$ group, S-101), Smopex-102 (-COOH group, S-102) were obtained from Johnson Matthey Turku, Finland. Silver wire (1 mm diameter, 99.9 % pure) was purchased from local supplier. Deionized water having a resistivity of 18 MΩ or greater was used in the study. All other chemicals used in the study were of analytical grade.

Preparation of electrodes

Silver–silver chloride electrodes were used for their stability and reversibility. The rod-shaped cathode was prepared by dipping the silver wire into the molten silver chloride to form thin and uniform coat **[20]**.

Preparation of rat skin

Wistar rat skin was used for the in vitro permeation study. After removal of hair, the rat was executed following the guidelines of the Committee for Control and Supervision of Experiments on Animal (CPCSEA), New Delhi, India. The skin was carefully excised; adhering fat and other visceral debris were removed manually. The skin was then put into refrigerator after washing by physiological saline and used within 3 days. The skin was washed with saline solution before starting the experiment. This experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC).

Drug loading into ion exchange material

The drug-resin and fiber complexes i.e. DRC-1 with I-204, DRC-2 with I-224, DFC-1 with S-102 and DFC-2 with S-101 were prepared by batch method **[21].** Complexes of each of the ion exchange resins and fibers with drug were prepared in 1:1 ratio. An accurately weighed amount (100mg) of SS was dissolved in water. Then known weight (100mg) of ion exchange resin and fibers was added to the solution separately. This mixture was stirred on magnetic stirrer for 4 h and filtered through Whatman filter paper. The complexes thus formed were washed with of water and dried in hot air oven. The drug content in the final filtrate was analyzed by UV-spectroscopy at 226 nm. The percent drug loading is calculated by the equation:

$$\%\ Drug\ loading = \frac{Amount\ of\ SS\ added - Amount\ of\ SS\ unloaded}{Amount\ of\ SS\ added} \times 100$$

Characterization of ion exchange material

The thermal behaviors of SS, S-101 and DFC-2 were studied on Shimadzu DSC 60 under flow of nitrogen gas of 40 ml/min and heating rate of 10°C per minute in the temperature range of 30°C to 300°C. Samples of 3 mg were weighed in a standard aluminum pan with a pinhole on the lid. An empty pan of the same type was used as reference. Bruker AXS D8 Advance Diffractometer with Cu, wavelength 1.5406 Å was used for X-ray diffraction measurements. X-ray diffraction pattern of SS, S-101, SS- S101 physical mixture and DFC-2 were studied.

Drug release study

Drug release from ion exchange material was studied in vertical typed Franz diffusion cell at 32°C with diffusion area of 1.76 cm^2. For this study, the synthetic barrier used was 0.22 µm cellulose acetate microporous membrane hydrated with receiver medium before experiments. The phosphate buffer saline (pH 7.4) was placed in receiver compartment of the diffusion cell. DRC-1, DRC-2, DFC-1 and DFC-2 (equivalent to drug 50 mg) were placed separately in donor compartment. The drug release from ion exchange material was studied in absence as well as in presence of external electric field (direct current 0.5mA/cm^2). In order to investigate whether the drug ions in the absence of other ions could be released from the drug ion exchange material complexes by the aid of electric filed force in the process of iontophoresis the same experiment was performed in deionized water.

In vitro permeation study

Permeation studies were performed in vertical type Franz diffusion cell at 32°C with diffusion area of 1.76 cm^2. The skin was hydrated for 2 h in phosphate buffer saline (pH 7.4) prior to mounting on the diffusion cell. To simulate in vivo situation receptor compartment was filled with phosphate buffer saline pH 7.4. DRC-2 and DFC-2 having $-SO_3H$ functional group were selected for in vitro permeation study because of their higher drug release and were placed in donor compartment. Permeation study was performed at passive as well as iontophoretic (direct current 0.5 mA/cm^2) transport conditions. The similar experiments carried out with the aqueous solution of drug without ion exchange material were the controls. The same experiment was repeated for DFC-2 by using a pulsed current having different duty cycles of 100, 70, 50, and 30 %.

Sample collection and data analysis

Aliquots of 2ml were collected for analysis from receiver compartment and replaced with the same volume of fresh receptor medium up to 8 h (1, 2, 3, 4, 6, 8 h). The samples collected were analyzed on suitable dilutions for the drug content at 226 nm on UV spectrophotometer. The transdermal flux (J_{SS}) was calculated from the slope of the linear portion of the curve. Q_8 is the cumulative amount of drug permeated per cm^2 of skin in 8 h. The enhancement ratio (ER) for the flux was calculated by the equation:

$$ER = \frac{Iontophoretic\ flux}{Passive\ flux}$$

Data obtained from experiments was subjected to one way / two ways ANOVA followed by Tukey's Multiple Comparisons Test with the significance level set at 0.05. The data were expressed as mean ± SD. (Graph Pad Prism 6.0)

Results and discussion

Drug loading

The percentage of drug loaded on ion exchange resins and fibers were determined. The per cent drug loading of DRC-1, DRC-2, DFC-1 and DFC-2 was determined to be about 61.50% ± 1.13, 39.36% ± 0.48, 78.72% ± 0.85 and 66.02% ± 0.52 and respectively i.e. DFC-1 > DFC-2 > DRC-1 > DRC-2. The observation that ion exchange fibers load more drug than the resins can be ascribed to availability of higher number of exchangeable groups on fibers owing to higher specific surface area of fibers and their non-crosslinked framework. When compared in fibers, SS shows more loading in DFC-1 where ion exchange fiber used possesses carboxylic acid functions than in DFC-2 where ion exchange fiber used possesses sulfonic acid function. This can be attributed to higher electronegativity of -COOH groups than $-SO_3H$. Moreover, the carbon atom in carboxylic acid being more electronegative than sulfur atom in sulfonic acid functional group, possess more

hydrophilic character that results in more affinity toward hydrophilic SS.

Characterization of ion exchange material DSC

DSC thermograms of SS, S-101 and DFC-2 are presented in **Fig. 2**. The thermogram of pure drug shows sharp endothermic peak at 165.43°C indicating its melting. The shift in the endothermic peak in the thermogram of the DFC-2 indicates formation of complex with ion exchange fiber.

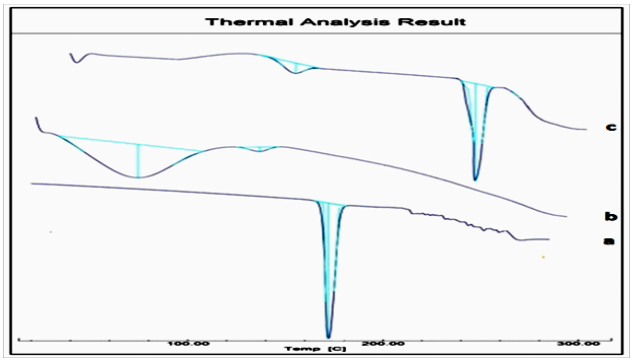

Fig. 2. DSC thermograms of (a) SS, (b) S-101, (c) DFC-2.

PXRD

Powder X-ray diffractograms of SS, S-101, SS-S101 physical mixture and DFC-2 are presented in **Fig. 3**. SS is a crystalline material, giving the sharp peaks in X-ray diffractogram. X-ray diffractogram shows S-101 is partly amorphous in nature. The physical mixture of drug with S-101 shows sharp peaks owing to the crystalline nature of SS and some diffused peaks of S-101.The absence of peaks of major intensity in DFC-2 as compared to physical mixture indicates loss of crystallinity of SS.

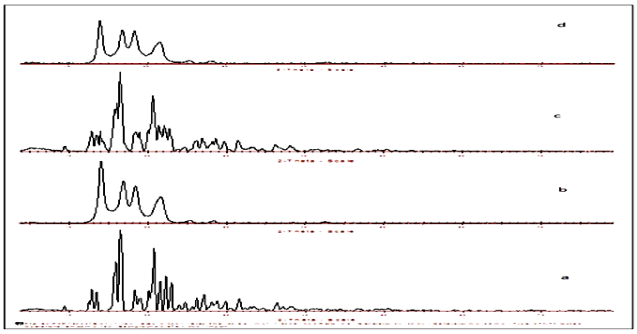

Fig. 3. Powder X-ray diffractograms of (a) SS, (b) S-101, (c) SS- S101 physical mixture, (d) DFC-2.

Drug release study

The ions from the receiver solution i.e. phosphate buffer saline pH 7.4 migrated into the donor compartment and exchange with the cationic SS which had been bound in ion exchange material (resin/fiber). The released SS then diffuses into receiver medium. The ion-exchange process is a diffusion process and is driven by the Donnan potential which is an electrical potential difference between the ion exchange phase and the external solution. This diffusion process continues till the Donnan equilibrium is reached, which is the equality of electrochemical potential for each mobile ion.

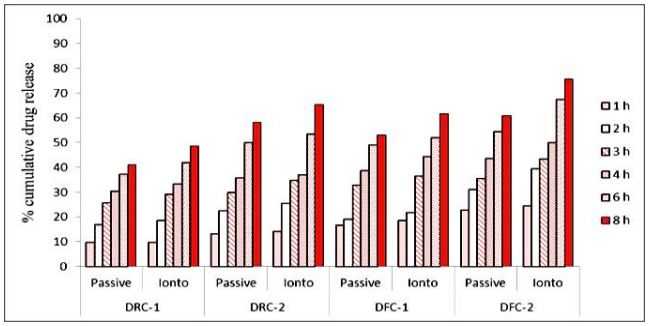

Fig. 4a. Comparison of release profiles of SS across cellulose acetate 0.22µm microporous membrane into phosphate buffer saline (pH 7.4).

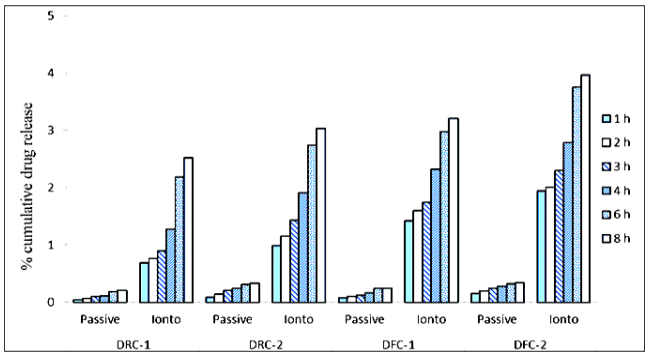

Fig. 4b. Comparison of release profiles of SS across cellulose acetate 0.22µm microporous membrane into water.

The release profiles of SS from DRC-1, DRC-2, DFC-1and DFC-2 with and without external electric field into phosphate buffer saline (pH 7.4) and water are shown in **Fig. 4a** and **Fig. 4b** respectively.

While comparing release profiles of resins and fibers having same functional group **Fig. 4a** showed that the percent drug release from fibers is higher than that from resins. This may be due to easier access of ions to the exchangeable groups located on the surface of the fibers. Since specific interaction of hydrophilic SS with -COOH group is stronger compared with $–SO_3H$ group, the percent drug release from DRC-1 and DFC-1 was comparatively lower than DRC-2 and DFC-2. **Fig. 4b** showed that percentage of drug released in water from complexes with the external electric field was higher than that without the external electric field. These results indicate that externally applied electric current also played an important role in releasing drug from ion exchange materials. Externally applied electric current overcomes the force of attraction between drug ions and the functional groups of ion exchange materials that resulted in drug release.

In vitro permeation study

Application of external electric field improves the permeation of the drug by the repulsion of the drug ions away from electrode of like charges. Application of iontophoretic voltage (< 10 V) reversibly alters the barrier properties of skin by reducing the resistivity of skin by one

to two orders of magnitude (from 100kΩ/cm^2) over a time scale of seconds to ten minutes **[22]**. Iontophoresis markedly improved the transdermal permeation of SS. On ionization, sumatriptan acquires a positive charge. On application of electric field the positive charge of the anode pushes positively charged sumatriptan ions into the skin; this is why its transport across the skin is increased as compared with passive diffusion.

The permeation profiles of SS from solution, DRC-2 and DFC-2 across rat skin with and without external electric field into phosphate buffer saline (pH 7.4) are shown in **Fig. 5**.

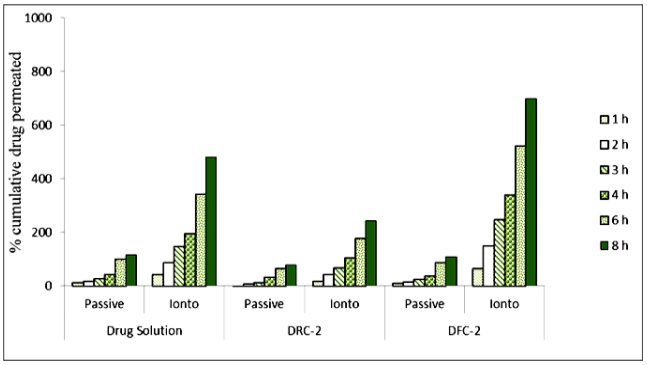

Fig. 5. Comparison of drug permeation profiles across rat skin into phosphate buffer saline (pH 7.4).

The order of permeation enhancement is as: DFC-2> Drug solution > DRC-2. In the case of DFC-2, the amount of permeated drug as well as transdermal flux of drug increased significantly compared to that of DRC-2 and plain drug solution, indicating that the DFC-2 increases the efficiency of drug ion's penetration assisted by iontophoresis. Since the ion exchange groups of resin are located within the spherical bead, rather than promoting the penetration across the skin, the ion exchange resin delayed release and penetration during the iontophoresis experiments. The effect of continuous current iontophoresis (0.5mA/cm^2) on permeation parameters is shown in **Table 1**.

Use of continuous direct current may result in skin polarization, which can reduce the efficiency of iontophoretic delivery proportional to the length of direct current application. The buildup of this polarizable current can be overcome by using pulsed direct current that is delivered periodically.

Table 1. Effect of continuous current iontophoresis on permeation parameters.

Form of drug as	Q_8 (μg/cm^2)		J_{ss}(μg/h cm^2)		ER	
	0 mA/cm^2 (Passive)	0.5mA/cm^2 (Iontophoresis)	0 mA/cm^2 (Passive)	0.5mA/cm^2 (Iontophoresis)	0 mA/cm^2 (Passive)	0.5mA/cm^2 (Iontophoresis)
Solution	117.25 ± 21.2	482.28 ± 35.2	5.30 ± 0.83	20.04 ± 2.61	1.000	3.78
DRC-2	77.51 ± 16.1	244.78 ± 29.5	3.70 ± 1.09	10.56 ± 2.56	1.000	2.85
DFC-2	107.44 ± 19.75	698.27 ± 37.9	4.77 ± 2.05	29.05 ± 3.41	1.000	6.09

Therefore, to further increase the permeation rate and the flux of SS across the skin, pulsed iontophoresis of DFC-2 was performed. **Fig. 6** shows the permeation profile of SS at pulsed iontophoresis at duty cycles of 100, 70, 50, 30 % and effect of pulsed iontophoresis on permeation parameter is shown in **Table 2**. The flux was significantly increased at the pulse of duty cycle 50 % (P<0.001) with a flux of 38.47 ± 2.40 μg/cm/h (**Table 2**).

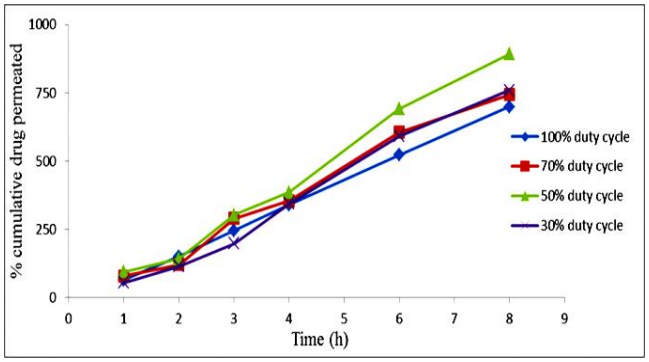

Fig. 6. Effect of continuous current and pulsed current iontophoresis on cumulative amount (μg/cm^2) of drug permeated across rat skin into phosphate buffer saline (pH 7.4).

The use of pulse current allows the skin to depolarize and return to its initial electric condition when the current phase is put off for a fraction of time. The order of permeation enhancement was: Continuous current 100 %< Pulsed current 70 % < Pulsed Current 30 % < Pulsed Current 50 %. This result could be explained by increase in off period of the pulse with decrease in duty cycle (ON: OFF ratio). The enhanced depolarization at 30 % duty cycle results in decrease in efficiency of drug transport compared to that with 50 % duty cycle. This may be due to the fact that with decrease in duty cycle off period of pulse increases which reduces the total amount of current passed through the skin.

Table 2. Effect of continuous and pulsed current iontophoresis on permeation parameters.

Current Profile	Q_8 (μg/cm^2)	J_{ss}(μg/h cm^2)	ER
0 mA/cm^2(passive permeation)	107.44 ± 12.2	4.77 ± 0.91	1.00
0.5 mA/cm^2 100% duty cycle (Continuous current)	698.27 ± 31.6	29.05 ± 1.45	6.09
0.5 mA/cm^2 70 % duty cycle (Pulsed current)	743.09 ± 28.3	32.25 ± 2.83	6.76
0.5 mA/cm^2 50 % duty cycle (Pulsed current)	891.72 ± 39.1	38.47 ± 3.59	8.06
0.5 mA/cm^{2}30% duty cycle (Pulsed current)	759.18 ± 26.9	34.17 ± 2.35	7.16

Effect of iontophoresis on drug permeation rate

In order to examine the effect of iontophoresis on drug permeation rate the variation of drug permeation rate at different time point was calculated using following equation **[23]**,

$$V = \frac{R_2 - R_1}{T_2 - T_1}$$

where, R_1 and R_2 are the amounts of drug permeated at time T_1 and T_2 as adjacent sampling time, V (μg/cm^2/h) is the drug permeation rate at time $(T_1 + T_2)/2$.

Fig. 7 shows the variation in permeation rate of drug from plain drug solution, DRF-2 and DRC-2. The variations of drug permeation rate in both DFC-2 and DRC-2 case were very small compared to that of drug solution. Though the DRC-2 shows less variation in drug permeation rate, it delays the drug release since the ion exchange groups of resins are located inside its structure. The smaller variations in case of DFC-2 indicate that

combining ion exchange fiber with iontophoresis will reduce the fluctuation of the drug permeation and enable a constant drug delivery.

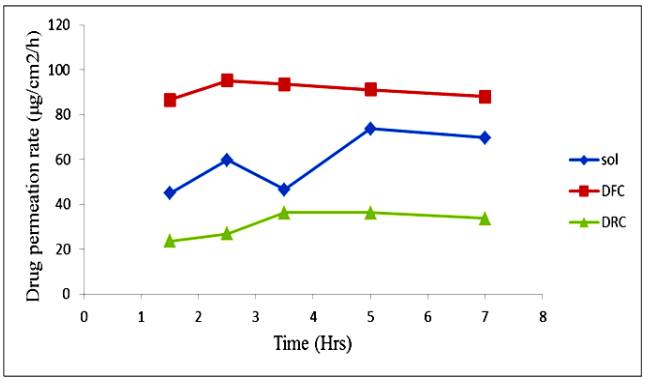

Fig. 7. The variation in iontophoresis drug permeation rate.

Conclusion

In the present study potential of ion exchange resins and fibers as drug carrier to enhance the transdermal permeation of SS in assistance with iontophoresis has been satisfactorily investigated. Two cationic ion exchange resins and two fibers were selected for the study. The drug-resin and fiber complexes *i.e*. DRC-1 with I-204, DRC-2 with I-224, DFC-1 with S-102 and DFC-2 with S-101 were prepared by batch method and compared for per cent drug loading, drug release and drug permeation. The order of per cent drug loading was DFC-1 > DFC-2 > DRC-1 > DRC-2. It was observed that the drug loading was higher with fibers compared to resins because of its larger surface area, smaller thickness and surface location of ion exchange groups. Although drug loading was higher with DFC-1, higher fractions of drug were released from DFC-2.In vitro study results showed that iontophoresis enhanced permeation of SS compared to passive permeation across rat skin. The amount permeated as well as transdermal flux of SS was significantly higher with DFC-2 compared to DRC-2 and plain drug solution. Due of periodic depolarization of skin, pulsed iontophoresis at 50% duty cycle with DFC-2 showed better flux enhancement compared to continuous current iontophoresis. From the study results it is concluded that DFC-2 with iontophoresis had great potential in reducing the fluctuation in drug permeation with constant drug delivery. To support the conclusions of the study further in vitro and in vivo permeation studies are being carried out across the human skin too. In summary, the loading and release of SS are higher with cation exchange fiber. The cation exchange fibers with iontophoresis not only improve the permeability of SS across skin but also provide controlled and predictable drug delivery.

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