Therapeutic Delivery

Transdermal iron replenishment therapy

Iron deficiency anemia is one of the major nutritional deficiency disorders. Iron deficiency anemia occurs due to decreased absorption of iron from diet, chronic blood loss and other associated diseases. The importance of iron and deleterious effects of iron deficiency anemia are discussed briefly in this review followed by the transdermal approaches to deliver iron. Transdermal delivery of iron would be able to overcome the side effects associated with conventional oral and parenteral iron therapy and improves the patient compliance. During preliminary investigations, ferric pyrophosphate and iron dextran were selected as iron sources for transdermal delivery. Different biophysical techniques were explored to assess their efficiency in delivering iron across the skin, and *in vivo* studies were carried out using anemic rat model. Transdermal iron delivery is a promising approach that could make a huge positive impact on patients suffering with iron deficiency.

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Application of drugs over intact skin to treat health ailments has been in practice for several centuries [1]. Transdermal drug delivery systems (TDDS) became very popular during the last few decades mainly due to the clear advantages over enteral and parenteral delivery [2]. Along with noninvasiveness, TDDS offer advantages including bypassing the liver to avoid first pass metabolism of drugs and ease of application with more patient compliance than other drug delivery systems. Since the introduction of the scopolamine patch in 1979, there has been a significant increase in the number of transdermal delivery systems available on the market to date and over a billion transdermal systems are manufactured every year [3].

Iron is the key nutritional element required for all living organisms and is involved in various metabolic processes and in the synthesis of DNA and RNA [4]. Iron is an integral part of hemoglobin which serves as carrier of oxygen from lungs to tissues [5]. Iron is also essential for cell growth and the typical adult human body contains an average of 3–4 g of iron. Due to its high redox potential, Iron acts as catalyst in redox reactions in various biological processes. Iron helps in the production of neurotransmitters in the brain and is useful for neural development as well [6,7].

Iron exists either in the free form or heme iron in the diet. The free iron from the diet is converted from ferric form to ferrous form in the intestinal lumen and gets transported into the enterocyte cells. Iron can be stored in intestinal enterocytes bound to ferritin or transported to blood. Once it enters the systemic circulation, iron binds to the serum protein, transferrin. Transferrin is responsible for the transport of iron and carries iron to bone marrow for hemoglobin synthesis and other tissues in the body. Iron homeostasis in the system is closely regulated as there is no physiological mechanism for iron excretion from the body. Excess iron accumulation in the system causes organ dysfunction by producing the reactive oxygen species through the Fenton reaction.

Iron deficiency anemia (IDA) is one of the major nutritional deficiency disorders affecting children and women of child bearing age [8]. Even to date, more than a quarter of world population is anemic and iron deficiency anemia is the major contributing fac-

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Key terms

Iron dextran: Accepted for parenteral delivery of iron.

Ferric pyrophosphate: Very stable noncolloidal iron source suitable for transdermal delivery.

Iontophoresis: Application of a constant electric current involves in the movement of charged drug species through the skin.

tor among all other anemia disorders [9]. Iron deficiency may result due to malnutrition, decreased iron absorption, use of erythropoietin stimulating agents and several other illnesses. One of the most common causes of IDA in adults is acute blood loss in gastrointestinal bleeding, trauma and surgery [10].

Replenishment of body iron stores via oral and parenteral iron therapy has been in practice for several decades. Oral iron formulations are the choice for first line therapy to replenish body iron stores. Oral iron salts that are in clinical practice include ferrous sulfate, ferrous gluconate, ferrous fumarate and carbonyl iron along with few other ferric salts. Ferrous iron salts are preferred over ferric salts because of their superior solubility and availability at the pH of the duodenum and jejunum. Standard oral iron therapy in adults includes administration of ferrous salt formulations three to four times a day (~ elemental iron content of 150–180 mg) [11]. Oral iron therapy is associated with severe gastric side effects and poor patient adherence due to unpleasant taste and odor of iron salts particularly in pregnant women and children [12–14]. Moreover, absorption of iron in the intestine is a carrier mediated mechanism and only a fraction of the total administered oral dose is bioavailable.

Parenteral iron therapy is recommended only in severe iron deficiency conditions because of its invasiveness and systemic side effects due to colloidal nature of the parenteral iron products. Parenteral iron formulations that are approved for clinical use include ferric carboxymaltose, iron dextran (ID), ferumoxytol, iron sucrose and sodium ferric gluconate. The iron overload with parenteral formulations was reported to cause anaphylactic reactions and rarely even mortality [15]. With all the disadvantages associated with oral and parenteral delivery of iron, there is a need for the development of an alternative and safe mode of administration of iron products. Transdermal delivery of iron could be a potential method of treating iron deficiency with advantages such as noninvasiveness, safety and patient compliance that this route could offer. Transdermal delivery of iron would be attractive to patients due to the fact that this route could overcome the potential gastric and systemic side effects associated with oral and parenteral delivery respectively.

Percutaneous absorption of iron across mouse skin from water-in-oil and oil-in-water emulsion type ointments containing iron chelates were reported in the past by Minato *et al.* [16]. In this study, Minato and colleagues evaluated the absorption of water soluble substances from hydrophilic and absorption-based ointments using radioactive iron complexes with ethylenediaminetetraacetic acid and cupferron as model substance. The average absorption of iron from water-in-oil ointment containing water soluble iron-ethylenediaminetetraacetic acid complex was approximately 80% while it was only approximately 55% from oil-in-water ointment. In the same study, iron absorption from Fe-cupferron, a lipid soluble chelate was reported to be very low. But there were no reports of any systematic study that explored the delivery of iron via skin for replenishment, until recently reported by our group. Transdermal iron replenishment using various passive and biophysical techniques that were reported so far is summarized here.

Passive delivery of iron compounds across skin

The major barrier for transdermal delivery of drugs is the presence of stratum corneum layer in the skin. The closely packed keratinocytes as well as the intercellular lipid bilayers offer resistance for permeation of polar drugs. Moderately lipophilic drugs are relatively more permeable than extremely hydrophilic and extremely lipophilic molecules. Moreover, the molecular weight of drugs should be <500 Da to be permeable across the skin. When the drug possesses all these properties, it would be ideal for transdermal delivery provided the dose required is not impractical [17,18].

In case of transdermal iron replenishment therapy, the choice of iron source is challenging because all the iron salts used in oral iron therapy are hydrophilic and the products approved for parenteral therapy are huge in size due to their colloidal nature. Moreover, the release of free iron from ionization of iron salts, in the systemic circulation is a major concern due to the risk of generation of reactive oxygen species following oxidative stress at cellular level. Therefore, a slow and prolonged delivery of iron would be appropriate to avoid oversaturation of transferrin and accumulation of free iron. Gupta *et al.* [19] explored the use of ferric pyrophosphate (FPP) as a source of iron for parenteral delivery. FPP, a hydrophilic iron salt with a high stability constant (log K_{stab} 22.3) was reported to be safe to administer as a slow dialysate in maintenance of hemodialysis patients and is capable of triggering direct transfer of iron to transferrin, between transferrin molecules and between transferrin and ferritin [19–21]. Subsequently, Murthy and coworkers

utilized the same for transdermal delivery. However, they found that the *in vitro* passive transdermal flux of FPP was poor due to its high molecular weight (745 Da) and hydrophilicity of FPP [22]. There was a tenfold increase in the amount of FPP permeated across delipidized epidermis suggesting perturbation of stratum corneum can lead to enhanced delivery of iron across skin. As expected, the ID completely failed to permeate across the skin even after prolonged duration [23]. Iron dextran used in these studies was a colloidal suspension with 5% iron and 20% dextran with an average molecular weight of approximately 90 kDa.

Vaka *et al.* [24] studied the effect of chemical permeation enhancers on the transdermal delivery of FPP. Permeation enhancers such as 5% v/v dimethyl sulfoxide, 2% v/v azone, 5% w/v menthol, 5% v/v ethanol, 4% v/v isopropyl myristate and 1% w/v sodium lauryl sulfate were used. The authors reported that there was no significant improvement in the amount of iron permeated across porcine epidermis even after 24 h, although they observed a decrease in the epidermal electrical resistance. Due to limited success in passive delivery of FPP, various biophysical techniques were explored subsequently for the transdermal delivery.

Biophysical techniques to enhance transdermal iron delivery

'Iron'tophoresis: iontophoretic delivery of iron

Constant current iontophoresis was explored initially as a potential technique to enhance the transdermal delivery of iron [22]. Iontophoresis is an application of small electric current to make continuous pathways in the skin for drug delivery. Anodal iontophoresis was investigated initially, but did not lead to significant enhancement of FPP across skin. FPP having a dominant negative charge could be delivered using cathodal iontophoresis across the skin. With cathodal iontophoresis, the transdermal flux of FPP increased proportionally with applied current density. The predictability and programmability of iontophoresis mediated delivery of FPP across *in vitro* rat skin was studied systematically.

The total amount of FPP delivered across rat skin was correlated well with the applied electrical dose and the slope of linear plot indicates the amount of FPP (µg/cm^2) permeated per unit increase in the electric dose (mAh/cm^2) (Figure 1). The dose of FPP delivered can be modulated by varying either current duration or current density. *In vivo* studies were carried out in hairless rats for 6 h using a current density of 0.5 mA/cm^2. The serum iron and % transferrin saturation (% TS) were measured before and after application of current protocol and there was a significant increase in both serum iron and % TS. FPP was also

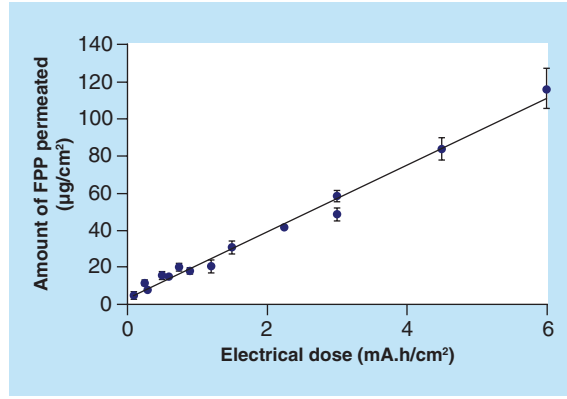

Figure 1. Correlation between the applied electrical dose (mAh/cm^2) and the amount of ferric pyrophosphate permeated (mg/cm^2) across hairless rat skin.
FPP: Ferric pyrophosphate.
Reproduced with permission from [22].

administered through intravenous route at different dose strengths and serum iron was measured. There was an increase in the serum iron concentration with increase in administered dose and the values returned to baseline after 24 h. The amount of FPP retained in the skin was also measured to see if iron forms a depot in the skin after iontophoresis. It was found that there was no significant difference between the iron content in the skin at active diffusion site and away from diffusion site indicating the poor tendency of iron to retain in the skin.

Constant voltage irontophoresis

In another study, Vaka *et al.* also explored the use of constant voltage iontophoresis to drive FPP across the porcine epidermis [24]. Three different constant volt-

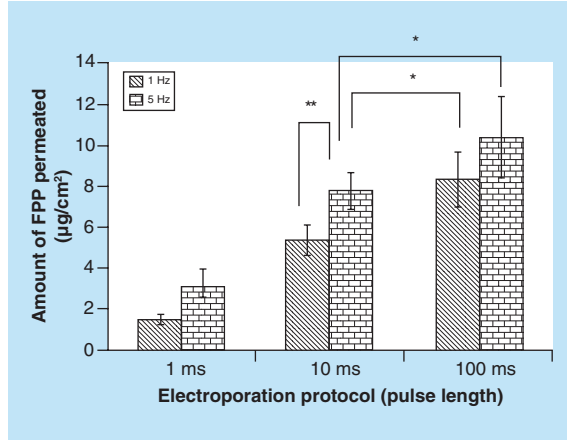

Figure 2. *In vitro* permeation of ferric pyrophosphate across porcine epidermis on application of 120 V and 100 pulses at different pulse lengths (1, 10 or 100 ms) and frequencies (1 or 5 Hz).
FPP: Ferric pyrophosphate.
Reproduced with permission from [24].

Table 1. Observed mean hematological and biochemical parameters in rats at healthy state and at anemic condition.

Parameter	Basal values	Anemic condition
Hematological parameters		
Hemoglobin (g/dl)	14.31 ± 2.47	10.58 ± 1.61†
HCT (%)	41.35 ± 8.33	32.4 ± 3.72†
MCV (fl)	56.25 ± 2.12	38 ± 2.86‡
MCH (pg)	19.56 ± 1.57	12.4 ± 1.22‡
MCHC (g/dl)	34.83 ± 1.61	28.22 ± 2.24§
RBC (10^{12}/l)	8.40 ± 0.83	6.61 ± 0.75†
RDWc (%)	16.71 ± 2.22	28.33 ± 2.73‡
Biochemical parameters		
Serum iron (μg/dl)	179.53 ± 15.84	83.46 ± 17.02‡
TIBC (μg/dl)	374.86 ± 56.33	483.84 ± 57.91†
% TS	46.28 ± 7.04	16.59 ± 2.11§
Lipid peroxidation (equivalent to MDA conc. [nmol/ml])	8.58 ± 1.72	14.51 ± 3.92†

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The difference in all parameters in rats between healthy (basal values) and anemic conditions is statistically significant.
†$p < 0.05$.
‡$p < 0.0001$.
§$p < 0.001$.
% TS: % transferrin saturation.

ages (0.5, 2 and 4 V) were applied for 30 min and there was approximately threefold and approximately tenfold increase in the permeation with 2 and 4 V respectively compared with the control, whereas 0.5 V was not effective. A significant drop in the electric resistance of the epidermis during the iontophoresis protocols was also observed.

Electroporation

Electroporation is the application of short high-voltage electric pulses that create transient porous pathways in the skin, which enable the transport of drugs across the skin. Electrical pulses with fixed voltage and number of pulses (120 V, 100 pulses) at different pulse lengths (1, 10 or 100 ms) and frequencies (1 or 5 Hz) were applied across porcine epidermis using an ECM 830 Electro Square Porator [24]. The receiver compartment fluid was sampled immediately and the amount of FPP delivered was measured. As shown in Figure 2, authors reported that a significant improvement in the permeation of FPP with an increase in frequency at 1 and 10 ms pulse lengths was observed. There was no significant difference in the amount of FPP permeated at pulse length of 100 ms with 1 Hz and 5 Hz frequencies. Moreover, there was no significant difference between the amount of FPP permeated with 10 and 100 ms protocols at different frequencies. Based on the observations, authors studied the combination of electroporation with constant voltage iontophoresis using 10 ms and 5 Hz protocol for electroporation.

Key terms

Electroporation: Application of high voltage electric pulses for short duration to create porous pathways in the skin.

Microneedles: Micron-sized needles capable of creating micropores in the upper layer of skin, thus allowing drugs to permeate across.

Electroporation in combination with constant voltage 'iron'tophoresis

Porcine epidermis was electroporated at 120 V, 100 pulses, 10 ms at 5 Hz and constant voltage iontophoresis was carried out. Voltage-dependent transport of FPP was observed and the amount of FPP delivered was significantly higher in case of electroporated epidermis compared with unelectroporated epidermis. There was a significant improvement (~two- to 42-fold) in the amount of FPP permeated with electroporation as a pretreatment protocol along with iontophoresis mediated delivery.

Iron delivery across microporated skin

Microneedles are micron-sized needles which have the ability to create micropores in the skin and aid in the creation of continuous pathways for drug delivery across the skin. Transdermal deliveries of FPP and ID were also studied across microporated hairless rat skin

in vitro and pharmacodynamic studies were carried out in hairless anemic rats [23,25].

The FPP flux across microporated rat skin was enhanced by approximately 11-fold after 6 h compared with passive flux. In the same experiment, the combination of constant current iontophoresis (0.3 mA/cm^2) along with microporation pretreatment was also studied. AdminPen® stainless steel microneedles (nanoBioSciences LLC., CA, USA) having an area of 1 cm^2 containing 187 microneedles with a needle height of 500 µm was used to create micropores in the skin. With the combination protocol there was approximately 44-fold increase in the flux of FPP compared with passive flux. The microneedles used in these studies were penetrated to a depth of 70 ± 10 µm into the skin which is mostly the upper layers of epidermis, that is, stratum corneum, confirming that the microneedles used were safe and do not invoke any sensory pain perception in the skin.

The recovery of micropores created by these microneedles was also evaluated with the help of transepidermal water loss studies using Vapometer® (Delfin Tech., Finland). There was an increase in the transepidermal water loss observed immediately after microporation from 13.6 ± 1.42 to 28.75 ± 2.68 g/m^2.h and the values returned to normal condition within 8–12 h in unoccluded condition indicating the pore closure.

Based on the *in vitro* results, *in vivo* studies were carried out in hairless rats by inducing iron deficiency anemia through iron deprivation in the diet. Iron deficiency anemia was induced within 5 weeks and the intensity of iron deficiency was measured with the help of various hematological (hemoglobin, mean corpuscular volume and red blood cell count, among others) and biochemical parameters (serum iron, total iron-binding capacity and % TS). The mean hematological and biochemical parameter values in healthy and anemic rats are given in Table 1.

Later, animals were divided into various groups and treatment protocol was initiated. For iontophoretic delivery a custom made patch (10 cm^2) was developed and FPP-HPMC gel was loaded on the patch and a current strength of 0.15 mA/cm^2 was applied. For combination of microporation with iontophoresis, rats were pretreated with microneedles for 2 min using 1 cm^2 array over a total of 10 cm^2 and iontophoresis was applied as described above. FPP administered through intraperitoneal route served as a positive control for this study. After 2–3 weeks of treatment, on alternative days for 4 h, there was a sig-

Table 2. The mean hematologic and biochemical parameters observed at the end of treatment period in rats administered with ferric pyrophosphate via different modes of administration.

Parameter	IN	MN	MN + IN[†]	IP
Hematological parameters				
Hemoglobin (g/dl)	10.42 ± 1.11	10.55 ± 0.9	13.12 ± 0.6[¶]	14.37 ± 0.41[¶]
HCT (%)	34.62 ± 2.45	28.67 ± 1.52	40.18 ± 4.24[¶]	42.0 ± 1.30[§]
MCV (fl)	39.2 ± 1.93	40.2 ± 1.4	46.45 ± 4.39[¶]	46 ± 1.73[§]
MCH (pg)	11.1 ± 1.16	13.14 ± 2.21	15.32 ± 2.51[¶]	15.8 ± 0.62[¶]
MCHC (g/dl)	30 ± 1.21	30.8 ± 2.44	32.9 ±1.39[¶]	34.3 ± 0.43[¶]
RBC (10^{12}/l)	7.05 ± 1.01	6.99 ± 1.10	7.72 ± 0.3[¶]	9.11 ± 0.15[¶]
RDWc (%)	25.73 ± 2.24	24.71 ± 3.43	22.58 ± 2.9[¶]	19.47 ± 2.23[§]
Biochemical parameters				
Serum Iron (µg/dl)	102.74 ± 10.22[¶]	109.52 ± 14.2[¶]	124.7± 8.8[§]	139.53 ± 13.6[#]
TIBC (µg/dl)	405.43 ± 21.67[¶]	399.5 ± 32.7[¶]	393.22 ± 25.3[¶]	354.81 ± 36.3[§]
% TS	25.3 ± 3.71[§]	29.47 ± 4.82[§]	31.86 ± 3.4[#]	39.37 ± 2.2[#]
Lipid peroxidation (equivalent to MDA conc. [nmol/ml])[‡]	13.13 ± 1.32	12.32 ± 2.54	12.42 ± 1.8	11.37± 2.2

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[†]The difference in all parameters (except lipid peroxidation) in MN + IN group animals after treatment is significantly different from those before treatment.
[‡]Not significant: there was no significant difference between lipid peroxidation levels at anemic condition and post treatment in all groups.
[§]$p < 0.001$.
[¶]$p < 0.05$.
[#]$p < 0.0001$.
IN: Iontophoretic treatment group; IP: Ferric pyrophosphate administered as intraperitoneal injection; MN: Microneedle treatment group; MN+IN: Iontophoresis combined with microneedle pretreatment.

Table 3. The mean values of hematological parameters prior to inducing anemia (healthy), after inducing anemia, after treating with ID in case of microneedle pretreatment, and after treating with ID via intraperitoneal route.

Hematological parameter	Healthy rats	Anemic condition	After microneedle pretreatment	Intraperitoneal group
Hemoglobin (g/dl)	14.43 ± 0.81	10.06 ± 1.05	13.96 ± 0.51	14.5 ± 0.22
RBC (*10^{12}/l)	8.59 ± 0.44	6.32 ± 0.59	10.25 ± 0.95	10.32 ± 0.25
Hematocrit (%)	42.65 ± 1.28	33.24 ± 3.37	41.87 ± 4.98	41.48 ± 0.91
Mean corpuscular volume (fl)	55.33 ± 4.12	45.31 ± 3.07	41.33 ± 2.25	46.03 ± 2.02
Mean corpuscular hemoglobin (pg)	19.30 ± 1.58	14.93 ± 0.68	14.86 ± 0.68	18.30 ± 0.75
Mean corpuscular hemoglobin concentration (g/dl)	35.39 ± 0.87	30.00 ± 1.83	32.03 ± 2.21	34.01 ± 0.73
Red blood cell distribution width (%)	16.47 ± 0.81	15.47 ± 3.87	16.73 ± 1.50	17.73 ± 0.73

ID: Iron dextran.
Reproduced with permission from [23].

nificant improvement in the hematological and biochemical parameters in combination protocol (microporation pretreatment with iontophoresis) group and intraperitoneal group compared with the values in anemic condition implying that microneedle pretreatment along with iontophoresis can deliver therapeutically required amount of iron in anemic rat models. Even though there was a slight improvement in the hematological and biochemical parameters in iontophoresis and microneedle pretreatment groups alone, the change was not significant, likely due to the subtherapeutic dose delivered in the specified treatment period. The mean hematological and biochemical parameters in all treatment groups are summarized and shown in Table 2.

Red blood cell morphology studies also proved that the microporation in combination with iontophoresis might be a potential safe technique to deliver iron to treat IDA. Lipid peroxidation studies were carried out to assess the safety of administered iron and there was no significant improvement in the lipid peroxidation values found after treatment compared with anemic state.

Delivery of iron dextran across microporated skin

The transdermal delivery of iron dextran with the help of microneedle pretreatment was evaluated *in vitro* across hairless rat skin for 6 h using vertical Franz diffusion cell set up. A cumulative amount of 10.28 ± 0.45 µg/cm^2 was permeated after 6 h from a 200 µl of 50 mg/ml donor solution across the skin. At the end of 6 h, 2.48 µg/mg of ID was found in the active diffusion area. As mentioned earlier, ID neither permeated in the skin nor retained in the skin when delivered passively. Based on the results, *in vivo* studies were carried out on anemic hairless rat models for 3 weeks on alternate days for 6 h. Rat skin was microporated with microneedles in an area of 10 cm^2 and a patch containing 200 µl of ID solution was applied and permeation studies were carried out. After 3 weeks of

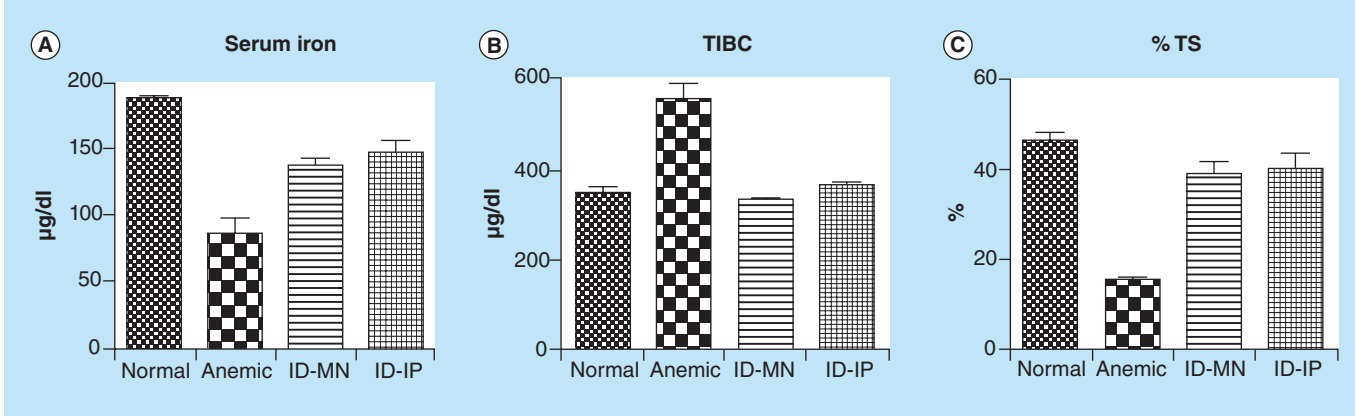

Figure 3. The mean values of all biochemical parameters, prior to inducing anemia (normal), after inducing anemia (anemic), after treating with ID (microneedle pretreatment [ID-MN]) and treatment with intraperitoneal injection of ID (ID-IP) [23].
ID: Iron dextran; ID-IP: ID-intraperitoneal injection; ID-MN: ID-microneedle; % TS: % Transferrin saturation.

treatment period, there was a significant improvement in the mean hematological and biochemical parameters and morphology of red blood cells in treatment group compared with the anemic condition. Iron dextran delivered via intraperitoneal route served as a positive control for this study. The mean hematological and biochemical parameters in different groups of animals are summarized in Table 3 and Figure 3.

The dermatokinetics of FPP following topical administration in the form of soluble microneedles was evaluated in hairless rats with the help of cutaneous microdialysis studies recently [N Modepalli *et al.* Unpublished Data]. These studies clearly demonstrated that when applied in the form of soluble microneedles, close therapeutic levels of iron could be delivered for the treatment of iron deficiency.

Conclusion

The passive delivery of FPP is poor due to its high molecular weight and hydrophilic nature. Various active biophysical techniques have been utilized to deliver iron across the skin. The studies have clearly indicated the need for combination approach to achieve close therapeutic doses of iron. Soluble microneedles appear to be a promising approach for the delivery of iron. However, more safety and toxicity studies need to be performed before iron replenishment can be implemented in clinical practice via transdermal route.

Future perspective

Passive transdermal delivery is limited to few active molecules with low molecular weight and moderate water solubility. For large molecules active techniques are needed to deliver therapeutically required quantities across skin. The efficacy of biophysical techniques like iontophoresis, electroporation and microporation was proved to deliver variety of active therapeutic agents across skin. In case of iron delivery, with the existing disadvantages of conventional drug delivery methods, we believe the noninvasive/minimal invasive delivery of iron via transdermal route would benefit sensitive patient groups like children, pregnant women and geriatric patients. Transdermal delivery of iron by these active techniques have the capability to overcome the disadvantages associated with conventional drug delivery techniques and can deliver effective therapeutic doses for treatment of iron deficiency anemia.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

The need for transdermal delivery of iron

- Oral iron therapy is often associated with severe side effects such as gastric intolerance, nausea and vomiting. Poor patient compliance is the most common disadvantage with oral iron formulations.
- Oral iron supplements have limited potential in treating anemia associated with conditions such as chronic blood loss, hemodialysis, malabsorption syndrome, Crohn's disease and inflammatory bowel diseases.
- Parenteral iron colloids are associated with immediate adverse events such as dyspnea, nausea and vomiting, fever, uticaria, hypotension, arthralgias and severe allergies. Fatal anaphylactic reactions were also reported.
- Repeated administration of parenteral iron formulations could be dangerous.
- Slow and prolonged delivery of iron has been suggested as the best suited way to avoid super saturation of transferrin.

Ferric pyrophosphate as iron source

- Hydrophilic iron salts used for oral therapy are not suitable for transdermal delivery due to risk of release of free iron ion in the systemic circulation.
- Parenteral iron colloids are huge in size and delivery of these agents across the skin passively is impractical.
- Ferric pyrophosphate is relatively stable compound with high stability constant (~log K_{stab} 22.3) with a moderate molecular weight. Moreover, its safety was also established parenterally in hemodialysis patients.

Biophysical techniques to enhance the delivery of iron across skin

- Passive delivery of ferric pyrophosphate was poor due to its hydrophilicity.
- Constant current and constant voltage iontophoresis, electroporation and microporation techniques were found to enhance the delivery of iron across the skin.
- Iontophoresis combined with microporation resulted in successful delivery of therapeutically required quantities of iron in anemic rat models.
- Iron colloids can also be delivered across skin with microporation technique. Soluble microneedles might be fean alternative and safe technique for delivering iron compounds.

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• **Highlights the importance of transdermal drug delivery systems in modern medicine and discusses the highlights of transdermal drug development systems at various stages in chronological order.**

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