SYSTEMATIC REVIEW	Iranian Biomedical Journal 29 (4): 189-205 May 2025

Transdermal Iontophoresis Insulin in Laboratory Animals: A Systematic Review

Zeinab Ahmadpour Emshi[1], Mohammad Mohsen Roostayi[2], Aliyeh Daryabor[2], Sedigheh Sadat Naimi[2*], Maryam Niajalili[1]

[1]Student Research Committee, Department of Physiotherapy, School of Rehabilitation, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Physiotherapy Research Center, Department of Physiotherapy, School of Rehabilitation, Shahid Beheshti Medical University, Tehran, Iran

OPEN ACCESS

Article type: Research Article
Received: June 18, 2025
Revised: July 8, 2025
Accepted: July 22, 2025
Published online: July 26, 2025

How to cite:
Transdermal Iontophoresis Insulin in Laboratory Animals: A Systematic Review. Ahmadpour Emshi Z, Roostayi MM, Daryabor A, Naimi SS, Niajallili M. *Iran. Biomed. J.* 2025; 29(4): 189-205.

ABSTRACT

Insulin therapy is essential for regulating glucose levels in diabetic patients. However, subcutaneous insulin injection, despite being a standard procedure, is invasive and often painful and can lead to complications such as skin damage and infections. These issues often result in poor patient compliance and inadequate glycemic control. Recently, transdermal insulin administration has been explored as an alternative to subcutaneous methods; however, no universally accepted protocol has been developed for its use. This systematic review aimed to evaluate the effect of iontophoresis on transdermal insulin administration in laboratory animals. Using the PICO search strategy and in accordance with PRISMA guidelines, relevant articles published from January 1980 to May 2025 were retrieved from Scopus, PubMed, ISI Web of Science, PEDro, Science Direct, and Google Scholar databases. The findings from these studies suggest that combining iontophoresis with physical enhancers of skin penetration can effectively regulate blood glucose levels while minimizing the risk of hypoglycemia. ***DOI: 10.61882/ibj.5127***

Keywords: Diabetes mellitus, Laboratory animals, Skin

Corresponding Author: Sedigheh Sadat Naimi
Physiotherapy Research Center, School of Rehabilitation, Shahid Beheshti University of Medical Sciences, Damavand street, Emam Hossein square, Tehran, 1616913111, Iran; Tel.: (+98-21) 77561408; Fax: (+98-21) 77561406; E-mail: naimi.se@gmail.com, naimi.se@sbmu.ac.ir.; ORCID ID: 0000-0001-7772-5737

INTRODUCTION

It is predicted that by 2030, one in 10 people worldwide will have diabetes. The disease will also affect one-third of the population in the United States. This situation poses a major challenge to global public health[1]. In the Middle East and North Africa regions—including Iran—the number of people with diabetes was estimated to be around 73 million in 2021. The most recent data from the IDF Diabetes Atlas (10th edition, 2021) indicates that by 2045, this figure is anticipated to rise to 136 million, a concerning 87% rise in the diabetic population[2].

Diabetes management is typically achieved through oral hypoglycemic drugs, subcutaneous insulin injections, or insulin pumps. The routes of insulin administration—subcutaneous, intravenous, or intramuscular—are selected based on the individual patient's needs and their clinical situation. Although continuous access to exogenous insulin is a safe and effective treatment for type 1 diabetes[3,4], it has its own disadvantages and challenges. The main disadvantage of oral drugs is their first-pass metabolism in the liver and degradation in the gastrointestinal tract[5,6], which significantly reduces their efficacy. Moreover, subcutaneous injections and insulin pumps can be painful and inconvenient due to the use of metal needles[7-9]. These challenges can result in poor control of glucose level and serious complications such as amputations and blindness[10]. To address these issues, various needle-free insulin delivery methods have been investigated[8-11]. One of the main obstacles to treatment

List of abbreviations:
DMPS: sodium 2, 3-dimercapto-1-propanesulfonate**, PICO:** the impact of patient, intervention, comparison, outcome; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses;

[DOI: 10.61882/ibj.5127]

is the low penetration of insulin into body tissues, which diminishes its bioavailability and effectiveness in clinical settings[12-14]. The transdermal delivery methods are less intrusive than painful subcutaneous injections for delivering insulin through the skin[15,16]. Additionally, the nasal, oral, and pulmonary techniques have also been applied. Transdermal insulin delivery protects the drug from enzymatic and chemical degradation in the GI tract[17], helps maintain glucose in steady state and encourages patients adherence[18].

In addition to chemical enhancement approaches, various physical technologies—including ultrasound, pyrojet injectors, iontophoresis, electroporation, microneedles, and thermal erosion—facilitate the transport of macromolecules across the skin[19]. Electroporation, an electrically assisted transdermal delivery method[20], along with other innovations such as sonophoresis, patches, vesicles, microemulsion, nanoparticles, and microdermabrasion, have been reviewed for insulin delivery[21].

Iontophoresis is a non-invasive technique that uses low current density (0.5 mA/cm^2) for 20-30 minutes to deliver drug molecules through the skin. Depending on the surface charge of the drug molecules, one electrode serves as either the cathode or the anode, while the other acts as the opposite[22]. In animal studies, iontophoretic insulin delivery has been shown to effectively reduce the blood glucose levels; however, applying this method in humans is more challenging due to higher insulin requirements and longer diffusion paths[23].

Transdermal insulin delivery is a promising alternative to subcutaneous injections for diabetes management[19,20,24]. This method protects insulin from degradation and allows for a controlled release pattern, improving patient compliance and hyperglycemia management[24]. Decades of research have led to various strategies for optimizing transdermal delivery by adjusting physical, physicochemical, and physiological parameters. This study aimed to identify the most effective protocol by systematically evaluating iontophoresis-based transdermal insulin delivery in laboratory animals. Following preclinical validation, the selected studies will focus on animal models to provide basic knowledge for future human applications.

MATERIALS AND METHODS

Search strategy

A PICO-based search strategy was conducted following PRISMA guidelines to identify relevant articles published between January 1990 and May 2025 (Fig. 1). Articles were collected from various databases and the specialized search engines including Scopus, PubMed, ISI Web of Science, PEDro, Science Direct, and Google Scholar. The initial search strategy was developed for PubMed and then adapted for other databases. Two independent reviewers conducted the literature search. Duplicate articles were removed using EndNote 20. The titles, abstracts, and full texts of the articles were screened independently by two researchers. Any discrepancies in the selection process were resolved through discussion between the researchers and, if necessary, a third reviewer was consulted.

Inclusion and exclusion criteria

This study included in vivo and in vitro experiments. All original articles were published in English and addressed iontophoresis and its effects on transdermal insulin delivery, regardless of their publication date. However, studies published only as abstracts, without access to the full text, were excluded.

Evaluation of methodological quality of selected articles

The methodological quality of the included preclinical studies was assessed using the modified Downs and Black Scale. This scale evaluates the quality, external validity, study bias, and statistical power of the study[25]. Each item was scored as “No” (zero), “Not determined” (zero), and “Yes” (one). The final scores for the 32 included studies are presented in Table 1.

Data extraction

Data extracted from the studies included laboratory sample characteristics, quality assessment scores, details of the interventions, control group information, obtained results, and key findings. These data are summarized in Table 1

RESULTS

A total of 1,244 relevant articles were identified during the initial search of the electronic databases. After screening the titles and abstracts, 134 articles were selected for further evaluation. Duplicates (n = 78) were removed, resulting in 32 articles that were directly related to the main objective of our study. These articles were selected by two authors of this review (Fig. 1). The studies were then analyzed for their relevance to the research question, reporting quality, and extracted data codes. All included studies were experimental animal studies (clinical trials) and had scored above 14 according to the modified Downs and Black assessment tool. Of a total score of 27, individual study scores ranged from 14 (poor) to 25 (good), with a mean score of 17 (fair). Specifically, 9 studies scored between 14 and 16 (poor), 4 scored 17 (fair), and 19 scored

[DOI: 10.61882/ibj.5127]

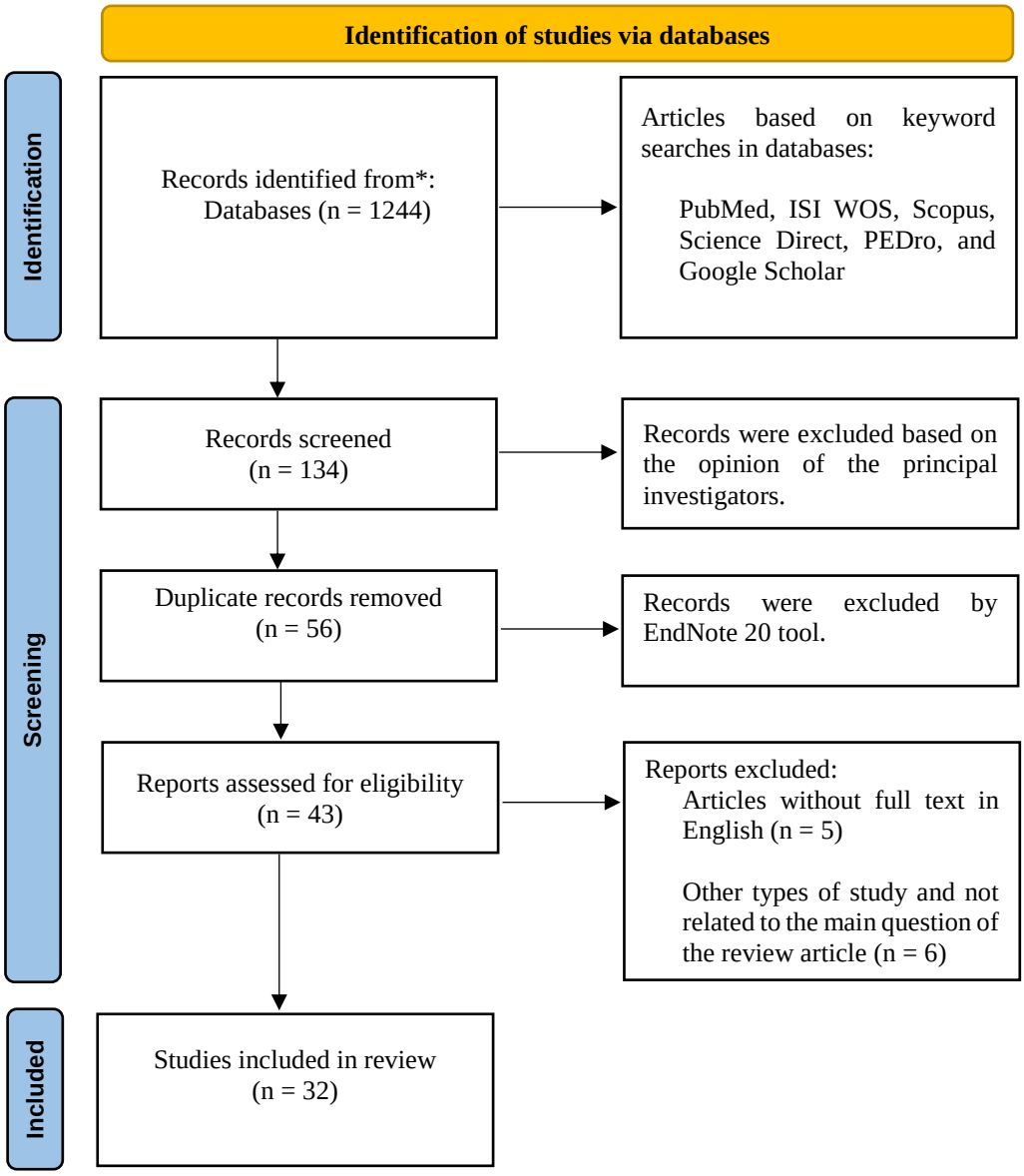

Fig. 1. Flowchart indicating the article selection process based on the PRISMA method. *From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71; For more information, visit: http://www.prisma-statement.org/.

between 18 and 25 (good). Overall, the majority of the studies demonstrated good methodological quality (Table 2).

Five studies focused on the epidermis of New Zealand white rabbits[26-30], four studies examined the epidermis of pork belly[31-34], two studies used guinea pigs[35,36], two studied human corpse skin[34,37], and one explored the skin of various laboratory animals[38]. The remaining studies employed laboratory mice, as well as male and female Sprague-Dawley and Wistar rats. Iontophoresis was the primary intervention used in all studies. However, several ones incorporated enhancement strategies, such as dermal patches[26,29], chemical enhancers[32,34,39,40], electrophoresis[41], electroporation[42], microneedles, and nanovesicles[29,36,38,43,44]. Among these studies, 8 were conducted in vivo, 13 were in vitro, and 10 employed both experimental approaches. Cheng et al. emphasized the importance of combining both in vivo and in vitro approaches[45]. Control group protocols varied across the included studies and encompassed passive diffusion and penetration[27,38,40,46-50], subcutaneous insulin injections[35,39,51], skin patches[26], iontophoresis[44], enhancement[52], absence of pretreatment while using chemical enhancers[31,32,37], and no therapeutic interventions[42,53,54]. The outcomes measured in the

[DOI: 10.61882/ibj.5127]

Table 1. Quality assessment of the included animal studies using the modified Downs and Black checklist

A	B	Jue-Chen	Meyer	Srinivasan	Chien	Banga	Cawley	Huang	Tomohira	Zakzewski	Langkjær	Kanikkannan	Pillai	Pillai	Pillai	Pillai	Rastogi	Pillai	Rastogi	Murthy	Panchagnula	Tokumoto	Chen	Rastogi	Kajimoto	Qin	Akram	Yang	Li, X. Huang	Li, J. Yang	Tari	Khamoushian	Wang
N.	**Number based on references**	**65**	**26**	**37**	**27**	**74**	**53**	**28**	**42**	**54**	**80**	**46**	**47**	**48**	**39**	**49**	**31**	**40**	**32**	**33**	**41**	**50**	**35**	**34**	**51**	**44**	**52**	**29**	**36**	**30**	**38**	**84**	**83**
	Reporting																																
Q1	Hypothesis/aim/ objective clearly described	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q2	Main outcomes in introduction or methods	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Q3	Patient characteristics clearly described	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q4	Interventions of interest clearly described	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q5	Principal confounders clearly described	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Q6	Main findings clearly described	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q7	Estimates of random variability provided for main outcomes	0	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	0	1	1
Q8	All adverse events of intervention reported	1	0	1	0	1	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0	1	1	1	0	1	1
Q9	Characteristics of patients lost to follow-up described	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Q10	Probability values reported for main outcomes	0	1	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0

[DOI: 10.61882/ibj.5127]

A	B	Jue-Chen	Meyer	Srinivasan	Chien	Banga	Cawley	Huang	Tomohira	Zakzewski	Langkjær	Kanikkannan	Pillai	Pillai	Pillai	Pillai	Rastogi	Pillai	Rastogi	Murthy	Panchagnula	Tokumoto	Chen	Rastogi	Kajimoto	Qin	Akram	Yang	Li, X. Huang	Li, J. Yang	Tari	Khamoushian	Wang
N.	**Number based on references**	**65**	**26**	**37**	**27**	**74**	**53**	**28**	**42**	**54**	**80**	**46**	**47**	**48**	**39**	**49**	**31**	**40**	**32**	**33**	**41**	**50**	**35**	**34**	**51**	**44**	**52**	**29**	**36**	**30**	**38**	**84**	**83**
	External validity																																
Q11	Subjects asked to participate were representative of source population	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q12	Subjects prepared to participate were representative of source population	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q13	Location and delivery of study treatment	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Internal validity–bias and confounding																																
Q14	Study participants blinded to treatment	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q15	Blinded outcome assessment	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	1
Q16	Any data dredging clearly described	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Q17	Analyses adjust for differing lengths of follow-up	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q18	Appropriate statistical tests performed	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q19	Compliance with interventions was reliable	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	1
Q20	Outcome measures were reliable and valid	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Q21	All participants recruited from the same source population	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

[DOI: 10.61882/ibj.5127]

A	B	Jue-Chen	Meyer	Srinivasan	Chien	Banga	Cawley	Huang	Tomohira	Zakzewski	Langkjær	Kanikkannan	Pillai	Pillai	Pillai	Pillai	Rastogi	Pillai	Rastogi	Murthy	Panchagnula	Tokumoto	Chen	Rastogi	Kajimoto	Qin	Akram	Yang	Li, X. Huang	Li, J. Yang	Tari	Khamoushian	Wang
N.	**Number based on references**	**65**	**26**	**37**	**27**	**74**	**53**	**28**	**42**	**54**	**80**	**46**	**47**	**48**	**39**	**49**	**31**	**40**	**32**	**33**	**41**	**50**	**35**	**34**	**51**	**44**	**52**	**29**	**36**	**30**	**38**	**84**	**83**
Q22	All participants recruited over the same time period	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Q23	Participants randomized to treatment(s)	NA	1	NA	NA	NA	1	0	1	1	0	0	NA	1	1	1	1	1	1	NA	NA	NA	NA	NA	1	NA	1	NA	1	1	NA	NA	NA
Q24	Allocation of treatment concealed from investigators and participants	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	1
Q25	Adequate adjustment for confounding	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Q26	Losses to follow-up taken into account	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
	Power																																
Q27	Sufficient power to detect treatment effect	NA	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
	TOTAL	**15**	**18**	**16**	**14**	**15**	**15**	**14**	**19**	**19**	**17**	**18**	**17**	**18**	**18**	**18**	**18**	**18**	**18**	**17**	**16**	**18**	**16**	**17**	**19**	**18**	**18**	**18**	**19**	**19**	**14**	**25**	**24**

The checklist consists of 27 items with a maximum possible score of 28. The total quality score for each study is presented as mean ± standard deviation (SD). Studies were categorized as high (score ≥ 20), moderate (score 15-19), or low (score < 15) quality

[DOI: 10.61882/ibj.5127]

Table 2. Key characteristics of the included animal studies

Ref.	Author (year)	Country	Quality score	Quality state	Sample	Test conditions	Intervention	Control group	Outcome measures	Conclusion
[65]	Jue-Chen (1988)	USA	15/27	Poor	Hairless rats (abdominal site)	In vivo	Iontophoresis	-	Blood glucose level	Two key parameters identified were frequency and current intensity. Applying a 1:1 on/off ratio resulted in improved regulation of blood glucose levels.
[26]	Meyer (1989)	USA	18/27	Good	(Albino rabbits)	In vivo	Patches containing insulin with/without iontophoresis	Patches containing an equal amount of insulin but without electrical current (passive)	Serum insulin level Blood glucose level	Statistically significant differences were observed between animals with active patches and control animals in both means and peak insulin responses ($p < 0.05$).
[37]	Srinivasan (1989)	USA	16/27	Fair	Hairless mouse skin (abdominal site) Full-thickness human skin	In vivo	Iontophoresis	Control experiments were conducted without ethanol pretreatment under identical conditions.	Skin permeability Flux	Performing iontophoresis following a two-hour pretreatment with 100% ethanol significantly increases the permeability coefficient of insulin across human skin.
[27]	Chien (1990)	USA	14/27	Poor	Hairless rat skin New Zealand white rabbits	In vivo In vitro	Iontophoresis	Passive diffusion	Skin permeation flux Blood glucose level Plasma insulin level	Pulsed direct current offers superior efficacy of conventional direct current on facilitating the transdermal iontophoretic delivery of peptide and protein-based medicines.
[74]	Banga (1993)	USA	15/27	Poor	Hairless rats (abdominal site)	In vivo	Iontophoresis	-	Blood glucose level Plasma insulin level	Extended application durations and higher donor concentrations of insulin were shown to enhance transdermal delivery when facilitated by iontophoresis.
[53]	Cawley (1996)	USA	15/27	Poor	Rats (abdominal and torso site)	In vivo	Pulsed iontophoresis	Rats did not receive insulin treatment; however, Nair® was applied to their skin on the day of the study.	Blood glucose level	In the group treated with Nair® on the day of the study, blood glucose levels decreased by an average of 68% after one hour of iontophoresis.
[28]	Huang (1996)	Taiwan	14/27	poor	Female New Zealand white rabbits (inner pinna skin)	In vitro	Iontophoresis	-	Permeation ratio of the degradation of insulin	During iontophoretic transdermal delivery, significant skin metabolism and electrical degradation were observed, especially at high temperature conditions. The rate of degradation was effectively reduced by decreasing the temperature or incorporating stabilizing agents.

[DOI: 10.61882/ibj.5127]

[42]	Tomohira (1997)	Japan	19/27	Good	Wistar female rats	In vivo	Iontophoresis (switching technique)	Non-switching iontophoresis	Blood glucose level	Combining electrical switching with the use of a chemical enhancer, such as urea, may offer dual benefits by enhancing transdermal absorption while minimizing skin irritation.
[54]	Zakzewski (1997)	USA	19/27	Good	Chronic diabetic rats (The torso and abdominal region)	In vivo	Pulsed iontophoresis	Control group animals received topical application of depilatory lotion on the day of the study and were placed in restraint cages for 80 minutes without insulin administration.	Blood glucose level	The concurrent application of depilatory treatment and passive insulin administration on the same day (with a 1-hour gap) led to a 29% decrease in blood glucose levels 1 hour post-insulin injection. In contrast, no significant difference ($p > 0.05$) was observed when depilatory was used alone or 24 hours before insulin administration."
[80]	Langkjær (1998)	USA	17/27	Average	Hairless mice (Full thickness dorsal skin)	In vitro	Iontophoresis	-	Flux	While human hexametric insulin exhibits minimal transdermal flux, monomeric insulin analogues bearing at least two additional negative charges can be effectively delivered across hairless mouse skin via iontophoresis.
[46]	Kanikkannan (1999)	India	18/27	Good	Wistar rats (abdominal region)	In vivo	Iontophoresis	Passive diffusion	Blood glucose level Plasma glucose level	Application of depilatory cream immediately prior to the experiment led to a significant reduction in plasma glucose levels through both passive diffusion and iontophoresis. Also, diabetic rats that received monomeric human insulin analog via undamaged (untreated) skin exhibited a substantial decrease in plasma glucose levels.
[47]	Pillai (2003)	India	17/27	Average	Male Sprague-Dawley rats	In vitro	Iontophoresis	Passive permeation experiments were used as control	Insulin concentration in the donor solution Flux	Optimizing the concentration and composition of competing ions in solution can enhance the transdermal transport efficiency of large peptides such as insulin.
[48]	Pillai (2003)	India	18/27	Good	Male Sprague-Dawley rats	In vitro	Iontophoresis	Passive permeation experiments	Insulin permeation (fluxes) Plasma glucose level	Insulin penetration and stability were significantly affected by the pH shift induced by platinum electrodes during iontophoretic delivery.
[39]	Pillai (2003)	India	18/27	Good	Female Sprague-Dawley rats	In vivo In vitro	Iontophoresis Chemical enhancers	To the control groups, a subcutaneous injection of	Plasma glucose level Permeation of insulin	Throughout the storage period, the poloxamer gel maintained both chemical and physical stability. In

[DOI: 10.61882/ibj.5127]

								insulin (1 IU / kg) was administered. The passive permeation experiments served as control in ex vivo studies.		ex vivo studies, linoleic acid and menthone demonstrated a synergistic improvement in insulin penetration when combined with iontophoresis.
[49]	Pillai (2003)	India	18/27	Good	Female Sprague-Dawley rats	In vitro	Iontophoresis with terpenes	Passive and iontophoresis were treated as controls for the respective groups.	Flux	The co-application of iontophoresis with terpene/ethanol formulation produced a synergistic improvement in insulin penetration, which was regulated by the type and concentration of the terpene used.
[31]	Rastogi (2003)	USA	18/27	Good	Epidermis of porcine ears	In vitro	Iontophoresis with depilatories	Untreated epidermis	Flux	Iontophoretic delivery resulted in a significant increase ($p < 0.05$) in insulin permeability across depilatory-pretreated epidermis, compared to untreated controls.
[40]	Pillai (2004)	India	18/27	Good	Female Sprague-Dawley rats	In vitro	Iontophoresis with chemical enhancers	Passive permeation experiments were used as control.	Flux	Combining iontophoresis with chemical enhancers targeting intercellular lipids could significantly improve the transdermal penetration of large peptides such as insulin.
[32]	Rastogi (2005)	USA	18/27	Good	Porcine ears Epidermis	In vitro	Chemical penetration Enhancer and iontophoresis	Epidermis without pretreatment was used as a control.	Flux	In compared to the untreated control epidermis, both passive and iontophoretic insulin transport were significantly enhanced ($p < 0.05$) through pig skin pretreated with fatty acids and limonene.
[33]	Murthy (2006)	USA	17/27	Average	Porcine belly skin	In vitro	Electroporation with DMPS and iontophoresis	Passive diffusion	Insulin transport	Combination of electroporation, anionic lipids, and electroosmosis could enable noninvasive in vivo insulin delivery at therapeutic levels, while also facilitating effective glucose extraction.
[41]	Panchagnula (2006)	India	16/27	Fair	Sprague-Dawley rats (dorsal skin)	In vitro	Iontophoresis anodal electrophoresis	-	Electrochemical stability of insulin Insulin concentration	The study highlighted the necessity of evaluating peptide/protein stability during iontophoretic optimization, as electrode-induced pH fluctuations can significantly influence the physical and chemical stability of the delivered biomolecules.
[50]	Tokumoto (2006)	Japan	18/27	Good	Male Sprague-Dawley rats	In vivo	Electroporation Iontophoresis	Passive diffusion	Blood glucose level Plasma insulin level	The synergistic effect of electroporation and iontophoresis was significantly affected by the conformational state of insulin in solution, with the inhibition of insulin aggregation further enhancing this effect.

[DOI: 10.61882/ibj.5127]

[35]	Chen (2009)	China	16/27	Fair	Male guinea pigs (dorsal portions) Male Sprague-Dawley rats	In vitro In vivo	Iontophoresis Microneedle Insulin-loaded nanovesicles	To the control groups, a subcutaneous injection of insulin (1.0 IU/kg) was administered.	Blood glucose levels	Charged nanovesicles exhibited significant transdermal penetration capabilities when assisted by physical enhancement techniques such as microneedles and iontophoresis.
[34]	Rastogi (2010)	USA	17/27	Average	Porcine epidermis Cadaver skin Male adult Wistar rats	In vitro In vivo	Chemical enhancers Iontophoresis	Diabetic control (normal saline intravenous)	Flux Blood glucose level	The controlled application of iontophoresis combined with a chemical enhancer blend resulted in a sustained reduction in blood glucose leve for eight hours.
[51]	Kajimoto (2011)	Japan	19/27	Good	Sprague-Dawley rats (dorsal skins)	In vitro In vivo	Liposomes Iontophoresis	Injection of insulin (i.p.)	Blood glucose level Plasma insulin concentration	Iontophoresis-driven Transfollicular delivery of drug-encapsulating liposomes could be useful for a broad range of therapeutics and is not limited to low-molecular-weight compounds.
[44]	Qin (2012)	China	18/27	Good	Sprague-Dawley Rats (abdominal skins)	In vitro In vivo	Microneedles and/or Iontophoresis (i.p.)	In the control group, only i.p. was applied for one hour on the intact skins.	Blood glucose level Insulin delivery	The use of micro conduits significantly improved transdermal insulin penetration and allowed for consistent basal delivery rates. A synergistic enhancement in insulin transport was observed when microneedles were combined with iontophoresis.
[52]	Akram (2013)	Pakistan	18/27	Good	Albino rats	In vitro In vivo	Iontophoresis Insulin emulgel formulation	Only insulin emulgel	Permeation flux Blood glucose level	Emu oil exhibits strong penetration-enhancing properties when combined with polysorbate 80 and isopropyl myristate, and its effectiveness is further amplified by the synergistic effect of iontophoresis.
[29]	Yang (2020)	China	18/27	Good	Rabbit skin Sprague-Dawley rats	In vitro In vivo	Smartphone-powered iontophoresis-microneedle Array patch	Vesicle	Insulin delivery Blood glucose level	This in vivo study has shown that the integrated microneedle-assisted platform offers controllability and delivery efficiency compared to conventional microneedle or iontophoretic insulin administration and induces significant hypoglycemic effects in a type-1 diabetic rat model.
[36]	Li, X. Huang (2021)	China	19/27	good	Pig skin Sprague-Dawley rat	In vitro In vivo	Microneedles Iontophoresis	Healthy rats without any treatments	Blood glucose level	Mesoporous microneedles enable efficient subcutaneous exchange of therapeutic substances by painlessly penetrating the stratum corneum. When integrated with iontophoresis, this system allows for precise electrical control, significantly enhancing both glucose and insulin delivery.

[DOI: 10.61882/ibj.5127]

[30]	Li, J. Yang (2021)	China	19/27	Good	New Zealand rabbit Sprague-Dawley rats	In vitro In vivo	Iontophoresis driven device	-	Mechanical test Blood glucose levels Serum insulin concentration	Iontophoresis-driven porous microneedle array patch achieved a 99% skin penetration rate, and maintained excellent biocompatibility without inducing skin irritation or hypersensitivity.
[38]	Tari (2021)	Iran	14/27	Poor	Various animal skins (rodent, pig, rabbi and snake)	In vitro	Iontophoresis Water-soluble Polypyrrole nanoparticles	Passive permeation experiments were performed as a control without applying any current	Blood glucose concentration	Effective surface absorption of loaded insulin onto water-soluble Polypyrrole nanoparticles. These insulin-loaded nanoparticles were utilized in in vitro studies to facilitate transdermal drug delivery across rat skin.
[84]	Khamoushian (2023)	Iran	25/27	good	Male diabetic rats (eight weeks old) induced with Streptozotocin Rat skin samples for in vitro study	In vitro In vivo	Insulin iontophoresis with skin pretreatment with eutectic solvents (ChCl/GLY and ChCl/EG) as chemical enhancers	PBS (pH 7.4) and ChCl/UR as controls	Q24h, insulin flux and Papp in in vitro studies In vivo reduction of blood glucose levels by up to 26% compared to baseline H&E staining for skin pathology	The combination of deep eutectic solvents, especially ChCl/EG and ChCl/GLY, with iontophoresis significantly increased transdermal insulin penetration and led to a marked reduction in blood glucose level in a diabetic animal model. No skin irritation or adverse reactions were observed.
[83]	Wang et al. (2025)	China	24/27	good	Streptozotocin - induced diabetic male mice (6–8 weeks) and 4T1 tumor-bearing mice	In vitro In vivo	Wearable iontophoresis device with microneedle patches containing insulin or glucagon or doxorubicin	-Group receiving only patch without current -Subcutaneous injection of insulin or PBS	•Blood glucose levels •Plasma insulin and glucagon concentrations •Tumor growth • Animal survival	Application of wearable transdermal device + incorporating indwelling patch led to a rapid and sustained reduction in blood glucose level, enhanced insulin absorption, effective hypoglycemia management, and notable inhibition of tumor growth. Iontophoresis demonstrated superior efficacy compared to patch application alone

Quality assessment was performed using the modified Downs and Black checklist, which evaluates the methodological quality of studies based on 27 criteria. The total possible score is 28, with higher scores indicating higher quality.

[DOI: 10.61882/ibj.5127]

selected studies included blood glucose levels, insulin flux, skin penetration rate, plasma insulin accumulation, insulin transfer rate, and electrochemical stability of insulin. Notably, none of the studies reported skin irritation. All studies demonstrated a reduction in blood glucose levels within hours and an increase in insulin penetration (Table 2).

DISCUSSION

In 2019, the estimated global death toll from diabetes was 4.2 million, which is equivalent to one death every seven seconds[55]. While subcutaneous insulin injection is currently the most effective method for regulating blood glucose level[56], it can have adverse effects, including inflammation, tissue death, pain, and microbial infections associated with injection process[55]. In contrast, transdermal drug delivery systems offer several advantages, such as ease of use, increased patient compliance, and a reduced risk of injection-related infections[57-59]. The skin serves as an excellent route for iontophoretic drug delivery due to its accessibility, large surface area, and well-characterized permeability properties[60,61].

Iontophoresis, first developed in the early 20th century, is a noninvasive, cost-effective, and portable method for transdermal drug delivery[62,63]. It allows for painless drug administration without damaging cellular tissues, making the treatment more acceptable to patients[43,64]. This review investigates the effect of iontophoresis on insulin delivery in animal models. Evidences suggest that iontophoresis can improve insulin penetration and maintain elevated glucose levels for hours without causing skin irritation.

In the process of iontophoresis, both direct and alternating currents are used to optimize insulin transport and mange glucose levels. The penetration of the drug through the skin is mainly influenced by several physical parameters, including the shape of the pulse wave, frequency, intensity, and density of the electric current (mA/cm²), active/inactive time ratios, duration of current application, and electrode placement methods[65]. In addition, chemical-physical factors such as acidity (pH), ionic strength of the environment, drug concentration, buffer solution composition, pretreatment of the skin, hair removal methods, and the use of microneedles also play significant roles[27]. These enhancement strategies can be classified into physical, physicochemical, and physiological categories.

During iontophoresis, two electrodes are placed between the skin and the capillaries beneath[66]. Positively charged molecules are repelled by the positive electrode (anode) and driven toward the capillaries. In contrast, negatively charged particles are repelled by the negative electrode (cathode) and the similarly charged capillary walls. This repulsion ultimately facilitates systemic absorption of the drug into the body[67]. The transport of ions across the skin layers occurs through two main mechanisms: electromigration and electroosmosis[62]. The efficiency of these processes is directly influenced by the strength of the applied electric field and the duration of contact[68,69]. Due to the natural negative charge of the skin, cationic drugs penetrate more rapidly, whereas the transdermal delivery of negatively charged insulin (~5800 Da) confers physiological challenges[70-75].

Extended treatment time has been found to prolong glycemic control and reduce the risk of hypoglycemia. Combining high frequencies with moderate currents has been shown to increase blood glucose-lowering effects, likely due to the reduction in skin electrical resistance. Studies have indicated that a 1:1 active/passive ratio at a frequency of 2000 Hz (equivalent to 0.5 ms per cycle) represents the optimal conditions. The type of waveform selected also significantly impacts the duration and pattern of blood glucose reduction. Research findings suggest that lowering current intensity, decreasing the duration of current application, and replacing continuous direct current with pulsed currents can significantly reduce blood glucose levels[65]. Although increasing current intensity, frequency, and treatment duration are mostly associated with improvements in blood glucose reduction, using very high current densities (<0.8 mA/m²) and high frequencies (<3000 Hz) does not yield proportional improvements in results[76]. To minimize electrochemical side effects such as skin irritation and burns[16,20,77,78], alternating current is considered a more suitable option due to its lower incidence of adverse effects[79]. Shorter durations of pulse current application, as opposed to continuous direct current, led to significant decrease in blood glucose levels, while lower current levels reduced skin toxicity and improved treatment efficacy[73]. This method significantly increased the permeability of the stratum corneum, allowing for better absorption of proteins[26]. However, it is important to note that increasing current density and temperature can accelerate the degradation of insulin during iontophoretic transdermal delivery[28]. Switching the polarity of the electrodes every 20 minutes has been demonstrated to improve the absorption of peptide drugs while reducing skin irritation, without compromising the efficiency of the extraction process[42].

Insulin degradation in skin homogenates and under experimental conditions poses challenges for in vivo studies. During iontophoresis, insulin accumulates in the skin and it is gradually released into the receiver

[DOI: 10.61882/ibj.5127]

medium. The efficiency of iontophoretic transdermal drug delivery systems can be improved by three main factors: adjusting the pH, increasing the duration of current application, and increasing the concentration of insulin in the donor compartment[74]. Studies have shown a direct relationship between the concentration of formulated insulin and its transdermal penetration rate. Specifically, adjusting the pH to 3.6, which is below the isoelectric point of insulin (5.2), resulted in the highest skin penetration[76]. Additionally, pH influenced the direction and intensity of the electroosmotic current, as well as the overall drug flux, which are dependent on the buffer composition and the polarity of the electrodes[49]. Two main factors affect pH: (1) the composition of the buffer, including the type and concentration of salts and (2) the inverse polarity of the electrodes. Notably, changes in pH caused by the operation of platinum electrodes significantly impacted insulin penetration and stability[48]. Sodium chloride concentrations up to 0.05 M improved insulin transport by inducing ionic convection, although higher concentrations may reduce efficacy[47]. Gel formulations, particularly Poloxamer 407, were compatible with iontophoresis and improve skin conformity and drug penetration[39].

Srinivasan and colleagues were the first to investigate the synergistic effect of iontophoresis combined with chemical enhancer pretreatment for delivering high molecular weight polypeptides. Their results showed that pretreating the skin with absolute ethanol for two hours before iontophoresis significantly increased insulin transport[37]. Cawley et al. found that the most rapid reduction in blood sugar occurred when a thioglycollate-based depilatory cream was applied on the day of iontophoresis. These depilatory creams destroy the hair structure in the subepidermal layer, allowing insulin to penetrate through the open hair follicles[53,54]. Furthermore, Rastogi et al. showed that depilatory creams such as Better Off, Marzena, and Sally Hansen significantly increased passive insulin flux compared with untreated epidermis[31]. These findings are consistent with the results reported by Kanikkannan et al.[46]. Langkjær and colleagues emphasized the importance of pretreatment by showing that simple cleansing with ethanol significantly improved the iontophoretic transfer of negatively charged monomeric insulin analogs. Gentle cleaning of the skin with absolute alcohol before iontophoresis removes surface lipids, reduces skin electrical resistance, and results in a 1000-fold increase in transdermal insulin transfer to the untreated skin[80]. Pillai et al. explored the use of terpenes for skin pretreatment and found that combining large peptides such as insulin with terpenes during iontophoresis produced a synergistic effect, with menthol/ethanol yielding the highest enhancement in transdermal insulin permeation[39]. In another study, the same author confirmed that chemical enhancers targeting extracellular lipids further improved the penetration of large peptides such as insulin during iontophoresis[40]. Additionally, Rastogi et al. reported significantly higher passive flux and insulin iontophoresis in limonene-treated pork epidermis compared to untreated controls, suggesting that therapeutic doses of insulin could be achieved with this combined approach[32]. Other enhancers contain DMPS[79], 1,8-cineole, oleic acid, and sodium deoxycholate in a propylene glycol/ethanol mixture (7:3)[34].

Various enhancement strategies—including electroporation, insulin-loaded nanovesicles, charged liposomes, insulin emulgel, and microneedles—have been successfully integrated with iontophoresis. The development of nanocarriers is the foundation of modern drug delivery systems. These carriers greatly increase the precision and efficacy of treatment by using two main strategies: "passive targeting" (such as the EPR effect) and "active targeting" (by binding a ligand to the surface)[81]. Studies have shown that the absorption of insulin using iontophoresis and electroporation alone is not effective enough. However, the combination of these two methods synergistically improved transdermal insulin delivery. Likewise, using insulin-containing nanovesicles with iontophoresis significantly enhanced insulin delivery by increasing the diffusion coefficient and partitioning. Transfollicular delivery of liposome-encapsulated drug molecules via iontophoresis has proven effective for a wide range of compounds, as demonstrated in a landmark study that first reported the potential of liposomes as carriers for transdermal drug delivery[51]. The combination of transdermal emulgel with iontophoresis also resulted in improved insulin absorption. Given the substantial research, iontophoretic delivery of insulin emulgel is considered an acceptable and painless alternative to injections[52]. However, these methods face several limitations. Key challenges include inadequate drug delivery, skin resistance, and insufficient peptide dosage. Safety issues such as skin irritation, erythema, pain, burns, adverse effects, and insulin accumulation further limit their applicability. Despite these challenges, numerous studies have suggested that iontophoresis can be a substitute for conventional methods[29,30,36,38]. In addition to new transdermal drug delivery methods, cell-based therapies—such as islet cell transplantation—are another approach to naturally controlling blood sugar. Recent advances in this field include techniques to more efficiently isolate these cells and the use of biomimetic hydrogels to protect them from immune system attack. The simultaneous

[DOI: 10.61882/ibj.5127]

development of these advanced drug delivery systems and cell protection methods reflects the extensive and multifaceted efforts of researchers to find an alternative to daily insulin injections[82]. Recent advances in iontophoresis technology have opened exciting new possibilities, which include its integration with deep eutectic solvents and the development of smart wearable systems that combine electrical stimulation, microneedling, and thermal technologies. The findings from studies in animal models have been remarkable, demonstrating not only a significant increase in insulin permeability but also a reduction in the natural resistance of the skin, which enables precise and controlled drug delivery. However, translating these promising preclinical results into clinical applications requires further investigation to address limitations such as skin irritation and the need for controlled drug delivery. Continued research is essential to validate these technologies and facilitate their progression toward clinical implementation[83, 84].

CONCLUSION

Iontophoresis is a promising method for non-invasive, programmed, and systemic delivery of peptide and protein drugs, including insulin. The pursuit of noninvasive strategies for diabetes management is a rapidly evolving field that encompasses a variety of approaches, from physical methods such as iontophoresis to biological interventions such as probiotic administration. Research evidence suggests that probiotics improve glycemic control by modulating the gut microbiota and its associated metabolic pathways. Recent advancements in iontophoresis systems and strategies to enhance their performance—including transdermal patches capable of delivering physiologic doses—have demonstrated that traditional barriers to transdermal drug delivery can be overcome. While the evidence presented in this review is largely based on preclinical studies, the initiation of human trials is a critical step toward clinical applications of this technology. A landmark clinical trial (ID: NCT05444842) entitled "Comparison of the Efficacy of Iontophoresis of Insulin Combined with Oleic Acid Versus Topical Insulin in Patients with Chronic Diabetic Foot Ulcers" (ClinicalTrials.gov) exemplifies the growing interest in utilizing iontophoresis technologies to address real-world therapeutic challenges. To fully realize the clinical potential of this technology, further human studies are recommended to validate the safety and effectiveness of delivering intact peptides into systemic circulation.

DECLARATIONS

Acknowledgments

The authors are grateful to Dr. Hamidreza Moghimi and Dr. Faraj Tabeie for their guidance, as well as The Student Research Committee of the Faculty of Rehabilitation Sciences of Shahid Beheshti University of Medical Sciences for their support of this research. AI Disclosure Statement: During the preparation of this work, the author(s) used QuillBot in order to rephrase sentences and improve the fluency and clarity of the English text. After using this tool, the author(s) thoroughly reviewed, edited, and approved the content and take full responsibility for the scientific content of the publication.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

Concept development: Sedigheh Sadat Naimi and Mohammad Mohsen Roostayi, Design: Sedigheh Sadat Naimi and Aliyeh Daryabor, Literature search: Sedigheh Sadat Naimi, Mohammad Mohsen Roostayi, and Aliyeh Daryabor, Quality assessment of articles: Ahmadpour Emshi Zeinab and Aliyeh Daryabor, Writing: Ahmadpour Emshi Zeinab and Maryam Niajalili, and Critical review: Sedigheh Sadat Naimi and Aliyeh Daryabor

Data availability

The datasets generated and/or analyzed during the current study are included in this published article (and its supplementary information files). (If the relevant data are not within the manuscript, please see the link)

Competing interests

The authors declare that they have no competing interests

Funding

No financial support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

[DOI: 10.61882/ibj.5127]

Supplementary information

The online version contains supplementary material.

REFERENCES

1. Yoo M, D'Silva LJ, Martin K, Sharma NK, Pasnoor M, LeMaster JW, et al. Pilot study of exercise therapy on painful diabetic peripheral neuropathy. Pain Med. 2015;16(8):1482-9.
2. Magliano DJ, Boyko EJ. IDF Diabetes Atlas. 10th edition. Brussels: International diabetes federation; 2021.
3. Owens DR, Zinman B, Bolli GB. Insulins today and beyond. Lancet. 2001;358(9283):739-46.
4. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: Effectiveness, complications, and resource utilization. JAMA. 1997;278(20):1663-9.
5. Larrañeta E, Lutton RE, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development. Mater Sci Eng. 2016;104:1-32.
6. Wang QL, Zhu DD, Chen Y, Guo XD. A fabrication method of microneedle molds with controlled microstructures. Mater Sci Eng C Mater Biol Appl. 2016;65:135-42.
7. Bae W-G, Ko H, So J-Y, Yi H, Lee C-H, Lee D-H, et al. Snake fang–inspired stamping patch for transdermal delivery of liquid formulations. Sci Transl Med. 2019;11(503):3329.
8. Ma G, Wu C. Microneedle, bio-microneedle and bio-inspired microneedle: A review. J Control Release. 2017;251:11-23.
9. Liu D, Yu B, Jiang G, Yu W, Zhang Y, Xu B. Fabrication of composite microneedles integrated with insulin-loaded CaCO3 microparticles and PVP for transdermal delivery in diabetic rats. Mater Sci Eng C Mater Biol Appl. 2018;90:180-8.
10. Wang J, Ye Y, Yu J, Kahkoska AR, Zhang X, Wang C, et al. Core–shell microneedle gel for self-regulated insulin delivery. ACS Nano. 2018;12(3):2466-73.
11. Owens DR, Zinman B, Bolli G. Alternative routes of insulin delivery. Diabet Med. 2003;20(11):886-98.
12. Khafagy E-S, Morishita M, Onuki Y, Takayama K. Current challenges in non-invasive insulin delivery systems: A comparative review. Adv Drug Deliv Rev. 2007;59(15):1521-46.
13. Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies. Nat Rev Drug Discov. 2014;13(9):655-72.
14. Yang R, Wei T, Goldberg H, Wang W, Cullion K, Kohane DS. Getting drugs across biological barriers. Adv Mater. 2017;29(37):1002.
15. Dharadhar S, Majumdar A, Dhoble S, Patravale V. Microneedles for transdermal drug delivery: A systematic review. Drug Dev Ind Pharm. 2019;45(2):188-201.
16. Simmons JA, Davis J, Thomas J, Lopez J, Le Blanc A, Allison H, et al. Characterization of skin blebs from intradermal jet injection: Ex-vivo studies. J Control Release. 2019;307:200-10.
17. Ita K. Transdermal iontophoretic drug delivery: Advances and challenges. J Drug Target. 2016;24(5):386-91.
18. Ita K. Perspectives on transdermal electroporation. Pharmaceutics. 2016;8(1):9.
19. Polat BE, Hart D, Langer R, Blankschtein D. Ultrasound-mediated transdermal drug delivery: Mechanisms, scope, and emerging trends. J Control Release. 2011;152(3):330-48.
20. Szunerits S, Boukherroub R. Heat: A highly efficient skin enhancer for transdermal drug delivery. Front Bioeng Biotechnol. 2018;6:15.
21. Ahad A, Raish M, Bin Jardan YA, Al-Mohizea AM, Al-Jenoobi FI. Delivery of insulin via skin route for the management of diabetes mellitus: Approaches for breaching the obstacles. Pharmaceutics. 2021;13(1):100.
22. Dixit N, Bali V, Baboota S, Ahuja A, Ali J. Iontophoresis-an approach for controlled drug delivery: A review. Curr Drug Deliv. 2007;4(1):1-10.
23. Tomoda K, Terashima H, Suzuki K, Inagi T, Terada H, Makino K. Enhanced transdermal delivery of indomethacin using combination of PLGA nanoparticles and iontophoresis in vivo. Colloids Surf B Biointerfaces. 2012;92:50-4.
24. Liang W, Pan HW, Vllasaliu D, Lam JK. Pulmonary delivery of biological drugs. Pharmaceutics. 2020;12(11):1025.
25. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84.
26. Meyer BR, Katzeff HL, Eschbach JC, Trimmer J, Zacharias SB, Rosen S, et al. Transdermal delivery of human insulin to albino rabbits using electrical current. Am J Med Sci. 1989;297(5):321-5.
27. Chien YW, Lelawongs P, Siddiqui O, Sun Y, Shi W. Facilitated transdermal delivery of therapeutic peptides and proteins by iontophoretic delivery devices. J Control Release. 1990;13(2-3):263-78.
28. Huang Y-Y, Wu S-M. Stability of peptides during iontophoretic transdermal delivery. Int J pharm. 1996;131(1):19-23.
29. Yang J, Li Y, Ye R, Zheng Y, Li X, Chen Y, et al. Smartphone-powered iontophoresis-microneedle array patch for controlled transdermal delivery. Microsyst Nanoeng. 2020;6(1):112.
30. Li Y, Yang J, Zheng Y, Ye R, Liu B, Huang Y, et al. Iontophoresis-driven porous microneedle array patch for active transdermal drug delivery. Acta Biomater. 2021;121:349-58.
31. Rastogi SK, Singh J. Passive and iontophoretic transport enhancement of insulin through porcine epidermis by depilatories: Permeability and Fourier transform infrared spectroscopy studies. AAPS PharmSciTech. 2003;4(3):1-9.
32. Rastogi SK, Singh J. Effect of chemical penetration

[DOI: 10.61882/ibj.5127]

enhancer and iontophoresis on the in vitro percutaneous absorption enhancement of insulin through porcine epidermis. Pharm Dev Technol. 2005;10(1):97-104.
33. Murthy SN, Zhao Y-L, Hui S-W, Sen A. Synergistic effect of anionic lipid enhancer and electroosmosis for transcutaneous delivery of insulin. Int J Pharm. 2006;326(1-2):1-6.
34. Rastogi R, Anand S, Dinda AK, Koul V. Investigation on the synergistic effect of a combination of chemical enhancers and modulated iontophoresis for transdermal delivery of insulin. Drug Dev Ind Pharm. 2010;36(8):993-1004.
35. Chen H, Zhu H, Zheng J, Mou D, Wan J, Zhang J, et al. Iontophoresis-driven penetration of nanovesicles through microneedle-induced skin microchannels for enhancing transdermal delivery of insulin. J Control Release. 2009;139(1):63-72.
36. Li X, Huang X, Mo J, Wang H, Huang Q, Yang C, et al. A fully integrated closed-loop system based on mesoporous microneedles-iontophoresis for diabetes treatment. Adv Sci. 2021;8(16):2100827.
37. Srinivasan V, Higuchi W, Sims S, Ghanem A, Behl C. Transdermal iontophoretic drug delivery: Mechanistic analysis and application to polypeptide delivery. J Pharm Sci. 1989;78(5):370-5.
38. Tari K, Khamoushian S, Madrakian T, Afkhami A, Łos MJ, Ghoorchian A, et al. Controlled transdermal iontophoresis of insulin from water-soluble polypyrrole nanoparticles: An in vitro study. Int J Mol Sci. 2021;22(22):12479.
39. Pillai O, Panchagnula R. Transdermal delivery of insulin from poloxamer gel: ex vivo and in vivo skin permeation studies in rat using iontophoresis and chemical enhancers. J Control Release. 2003;89(1):127-40.
40. Pillai O, Nair V, Panchagnula R. Transdermal iontophoresis of insulin: IV. Influence of chemical enhancers. Int J Pharm. 2004;269(1):109-20.
41. Panchagnula R, Bindra P, Kumar N, Shanker Dey C, Pillai O. Stability of insulin under iontophoretic conditions. Pharmazie. 2006;61(12):1014-8.
42. Tomohira Y, Machida Y, Onishi H, Nagai T. Iontophoretic transdermal absorption of insulin and calcitonin in rats with newly-devised switching technique and addition of urea. Int J pharm. 1997;155(2):231-9.
43. Thirunavukkarasu A, Nithya R, Jeyanthi J. Transdermal drug delivery systems for the effective management of type 2 diabetes mellitus: A review. Diabetes Res Clin Pract. 2022:194:109996.
44. Qin G, Gao Y, Wu Y, Zhang S, Qiu Y, Li F, et al. Simultaneous basal-bolus delivery of fast-acting insulin and its significance in diabetes management. Nanomedicine. 2012;8(2):221-7.
45. Cheng Y, Gong X, Yang J, Zheng G, Zheng Y, Li Y, et al. A touch-actuated glucose sensor fully integrated with microneedle array and reverse iontophoresis for diabetes monitoring. Biosens Bioelectron. 2022;203:114026.
46. Kanikkannan N, Singh J, Ramarao P. Transdermal iontophoretic delivery of bovine insulin and monomeric human insulin analogue. J Control release. 1999;59(1):99-105.
47. Pillai O, Borkute SD, Sivaprasad N, Panchagnula R. Transdermal iontophoresis of insulin. II. Physicochemical considerations. Int J Pharm. 2003;254(2):271-80.
48. Pillai O, Kumar N, Dey CS, Borkute S, Nagalingam S, Panchagnula R. Transdermal iontophoresis of insulin. Part 1: A study on the issues associated with the use of platinum electrodes on rat skin. J Pharm pharmacol. 2003;55(11):1505-13.
49. Pillai O, Panchagnula R. Transdermal iontophoresis of insulin. V. Effect of terpenes. J Control Release. 2003;88(2):287-96.
50. Tokumoto S, Higo N, Sugibayashi K. Effect of electroporation and pH on the iontophoretic transdermal delivery of human insulin. Int J Pharm. 2006;326(1-2):13-9.
51. Kajimoto K, Yamamoto M, Watanabe M, Kigasawa K, Kanamura K, Harashima H, et al. Noninvasive and persistent transfollicular drug delivery system using a combination of liposomes and iontophoresis. Int J Pharm. 2011;403(1-2):57-65.
52. Akram M, Naqvi SB, Khan A. Design and development of insulin emulgel formulation for transdermal drug delivery and its evaluation. Pak J Pharm Sci. 2013;26(2):323-32.
53. Cawley P, Zakzewski C, Wasilewski J, Ford W. Effect of skin preparation on transdermal insulin delivery. IEEE. 1996:50-1.
54. Zakzewski C, Wasilewski J, Cawley P, Ford W. Electrically enhanced transdermal delivery of insulin to chronic diabetic rats.IEEE. 1997:756813.
55. Federation ID: IDF diabetes atlas 9th edition. Http://www.Idf Diabetes Atlas. 2015.
56. Rawat S, Vengurlekar S, Rakesh B, Jain S, Srikarti G. Transdermal delivery by iontophoresis. Indian J Pharm Sci. 2008;70(1):5-10.
57. Whitley HP, Lee R, Steil C, Pillion D. Student pharmacists' service-oriented learning at a camp for children with type 1 diabetes mellitus. Cur Pharm Teach Learn. 2019;11(8):825-31.
58. Lee H, Song C, Baik S, Kim D, Hyeon T, Kim D-H. Device-assisted transdermal drug delivery. Adv Drug Deliv Rev. 2018;127:35-45.
59. Anselmo AC, Gokarn Y, Mitragotri S. Non-invasive delivery strategies for biologics. Nat Rev Drug Discov. 2019;18(1):19-40.
60. Nayak AK, Hasnain MS, Aminabhavi TM, Torchilin VP. Systems of nanovesicular drug delivery: Nanovesicular systems in drug delivery. London: Elsevier Academic Press; 2022.
61. Junaid MSA, Banga AK. Transdermal delivery of baclofen using iontophoresis and microneedles. AAPS PharmSciTech. 2022;23(3):84.
62. Pikal MJ. The role of electroosmotic flow in transdermal iontophoresis. Adv Drug Deliv Rev. 2001;46(1-3):281-305.
63. Matos BN, Pereira MN, Bravo M, Cunha-Filho M, Saldanha-Araújo F, Gratieri T, et al. Chitosan nanoparticles loading oxaliplatin as a mucoadhesive topical treatment of oral tumors: Iontophoresis further

[DOI: 10.61882/ibj.5127]

enhances drug delivery ex vivo. Int J Biol Macromol. 2020;154:1265-75.
64. Sakunpongpitiporn P, Naeowong W, Sirivat A. Enhanced transdermal insulin basal release from silk fibroin (SF) hydrogels via iontophoresis. Drug Deliv. 2022;29(1):2234-44.
65. Jue-Chen L, Ying S, Siddiqui O, Wei-min S, John L. Blood glucose control in diabetic rats by transdermal iontophoretic delivery of insulin. Int J Pharm. 1988;44(1-3):197-204.
66. 66. Vadlapatla R, Wong EY, Gayakwad SG. Electronic drug delivery systems: An overview. J Drug Deliv Sci Technol. 2017;41:359-66.
67. Banga A, Chien YW. Iontophoretic delivery of drugs: fundamentals, developments and biomedical applications. J Control Release. 1988;7:1-24.
68. Lau DT, Sharkey JW, Petryk L, Mancuso FA, Yu Z, Tse FL. Effect of current magnitude and drug concentration on lontophoretic delivery of octreotide acetate (Sandostatin) in the rabbit. Pharm Res. 1994;11(12):1742-6.
69. Sieg A, Jeanneret F, Fathi M, Hochstrasser D, Rudaz S, Veuthey J-L, et al. Extraction of amino acids by reverse iontophoresis in vivo. Eur J Pharm Biopharm. 2009;72(1):226-31.
70. Naik A, Kalia YN, Guy RH. Transdermal drug delivery: Overcoming the skin's barrier function. Pharm Sci Technol Today. 2000;3(9):318-26.
71. Sage Jr BH. Insulin iontophoresis. Pharm Biotechnol. 1997:10:319-41.
72. Stephen RL, Petelenz TJ, Jacobsen SC. Potential novel methods for insulin administration: I. Iontophoresis. Biomed Biochim Acta. 1984;43(5):553-8.
73. Chien YW, Siddiqui O, Sun Y, Shi WM, Liu JC. Transdermal iontophoretic delivery of therapeutic peptides/proteins I: insulin. Ann N Y Acad Sci. 1987;507:32-51.
74. Mao X, Liang B, Fang S. Reduced blood glucose in diabetic rats by pulse current iontophoretic transdermal delivery of insulin. Chin Pharm J. 1995;30(11):660-3.
75. Chien YW, Banga AK. Characterization of in vitro transdermal iontophoretic delivery of insulin. Drug Dev Ind Pharm. 1993;19(16):2069-87.
76. Mao XM, Liang BW, Fang ZS, Li Q, Yao YP, Zhou MW. Facilitated transdermal delivery of insulin by pulse current iontophoresis. Yao Xue Xue Bao. 1995;30(4):302-6.
77. Bakshi P, Vora D, Hemmady K, Banga AK. Iontophoretic skin delivery systems: Success and failures. Int J Pharm. 2020;586:119584.
78. Fukuta T, Oshima Y, Michiue K, Tanaka D, Kogure K. Non-invasive delivery of biological macromolecular drugs into the skin by iontophoresis and its application to psoriasis treatment. J Control Release. 2020;323:323-32.
79. Peña-Juárez MC, Guadarrama-Escobar OR, Escobar-Chávez JJ. Transdermal delivery systems for biomolecules. J Pharm Innov. 2021;17(2):319-32..
80. Langkjær L, Brange J, Grodsky GM, Guy RH. Iontophoresis of monomeric insulin analogues in vitro: Effects of insulin charge and skin pretreatment. J Control Release. 1998;51(1):47-56.
81. Wang H, Cai R, Wang S, Yang Y, Sheng T, Zhang W, et al. A wearable transdermal device for on-demand drug delivery. Matter. 2025;8(4):102040.
82. Khamoushian S, Madrakian T, Afkhami A, Ghoorchian A, Ghavami S, Tari K, et al. Transdermal delivery of insulin using combination of iontophoresis and deep eutectic solvents as chemical penetration enhancers: In vitro and in vivo evaluations. J Pharm Sci. 2023;112(8):2249-59.

[DOI: 10.61882/ibj.5127]