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Research Article

Pharmacokinetic Study of Novel Drug Delivery Systems for Insulin Administration in Diabetic Patients

Dr. Keya De Mukhopadhyay[1], Dr. Varada Vidya Rani[2*], Dr. Hariballav Mahapatra[3]

[1]Department of Biotechnology, Institute of Engineering and Management, New Town, University of Engineering and Management, Kolkata, Keya.
[2]Pediatrician, Aralaguppe Mallegowda District Hospital*
[3]Consultant Diabetologist, Sevayan Diabetes Centre, Puri, Shree Hospitals, Bhubaneswar

Abstract
Diabetes requires constant insulin delivery systems, but the current methods like subcutaneous injections and insulin pumps are not ideal as they are slow and have erratic absorption profiles. Other newer forms of insulins that have been developed are oral insulin, trans-dermal insulin, insulin inhaler, and implantable insulin delivery systems; all of which have the aim of enhancing the pharmacokinetics of insulin. In this paper, these new delivery systems were compared with the conventional delivery systems based on bioavailability, onset of action, and patient compliance, and the idea of gene therapy was also presented as a revolutionary concept. The research was a four-arm, randomized crossover clinical trial on 50 diabetic patients with 30 Type 1 and 20 Type 2 patients where the patients were administered subcutaneous injections, microneedle patches, oral insulin capsules, and inhalable insulin in a cross-over design with wash-out periods. The study showed that all the novel systems improved the bioavailability and the absorption rates and of all the systems inhaled insulin was the fastest acting with the (Tmax 0. Microneedle patches were also effective; however, conventional injections provided better glycaemic control and longer durability. In the future, it is possible to reduce or even exclude the external insulin requirement due to gene therapy, in other words, modification of patient cells to produce insulin. From these findings, we can conclude that although new systems have considerable benefits gene therapy might be the direction for long-term diabetes management.

Keywords: Insulin delivery, pharmacokinetics, novel drug delivery systems, gene therapy, diabetes management, bioavailability.

Author for correspondence: Email:- varadavidyarani@gmail.com

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INTRODUCTION

Diabetes mellitus is an extensive chronic metabolic disease that is prevalent among many people across the world. The condition is defined by the presence of high blood glucose levels for a prolonged time owing to disorders in insulin secretion or insulin sensitivity. Insulin is a hormone synthesized by the pancreas which plays an important role in the metabolism of glucose as it enables the cells to take up glucose from the bloodstream for energy. When there is insufficient insulin, as in type 1 diabetes, or when insulin resistance occurs in cells, as in type 2 diabetes, glucose elevates in the blood and brings about a variety of acute and long-term complications (Tan et al., 2019). Some of these complications are cardiovascular diseases, kidney failure, neuropathy, and retinopathy, and therefore; diabetes management is a core aspect of the health sector (Ogurtsova et al., 2021). Control of diabetes especially in patients who require insulin, depends on the use of insulin to regulate blood glucose levels. Insulin therapy is one of the oldest therapeutic measures that has been in use for the management of diabetes since 1921. Despite its effectiveness, traditional methods of insulin delivery subcutaneous injections, present several problems. Patients with diabetes need to take multiple injections in a day which can be very uncomfortable and cumbersome. This cyclical and intrusive style of intervention can result in low concordance

with insulin treatment and thus a negative impact on people's glycaemic management and the potential for complications (Davies et al., 2018). Additionally, insulin injections cause several complications such as lipodystrophy, localized infections, and unpredictable rate of insulin absorption that leads to erratic blood glucose levels (Aronson, 2012). Due to the necessity of developing other methods of insulin delivery, the idea of new drug delivery systems has been studied widely (Zhao et al., 2020). These new systems are meant to replace or at least reduce the need for conventional injections as they are said to be more patient-friendly, noninvasive, or minimally invasive. These new systems can therefore help to optimize the pharmacokinetic properties of insulin including its absorption, distribution, metabolism, and excretion process, and thus help to increase the effectiveness of diabetes management. Among all the possibilities of insulin delivery, one of the most perspective directions is the creation of oral insulin preparations (Iyer et al., 2022). Of all the methods used to administer a drug, the oral route is considered the best because of its convenience and patient compliance. However, injecting insulin into the bloodstream is very difficult because the digestive system is geared to degrade proteins such as insulin before they can be absorbed into the bloodstream. Insulin is susceptible to enzymatic degradation in the stomach and small intestine and if it is not degraded it has a large molecular size which cannot easily pass through the intestinal wall into the blood. Newer technologies in formulation and biotechnology have enabled the formulation of oral insulin delivery systems that have protective coatings, inhibitors of enzymes, and permeation enhancers to increase the bioavailability of insulin (Hirlekar, 2017). These formulations are intended to coat the insulin and prevent it from being broken down, as well as to allow the insulin to pass through the skin and enter the bloodstream without the need for a needle – thus bringing the dream of non-invasive diabetes care closer to reality. Another new idea is using of transdermal insulin delivery system to administer insulin using patches or microneedles. This method is painless, hence eliminating the pain and anxiety that are associated with normal injection procedures. Transdermal systems can also deliver insulin in a more controlled and sustained manner which may better help to control blood sugar levels and decrease the incidence of hypoglycemia. Modern advancements in transdermal delivery are the microneedle arrays that produce channels in the skin for the direct administration of insulin to the systemic circulation without being painful to the patient (Chen et al., 2015). Furthermore, other improvements in the formulation technologies like chemical permeation and nanoparticle carriers have made transdermal insulin delivery more effective and reproducible (Prausnitz & Langer, 2008). Another new solution is inhalable insulin which would be useful in patients who need rapid-acting insulin to manage postprandial blood glucose. The inhalable insulin is in the form of dry particles that are inhaled with the help of an inhaler through the lungs and the insulin particles are directly assimilated into the blood system. The lungs have a vast extent of absorptive surface for the drug and a thin alveolar barrier for the rapid and efficient uptake of insulin. Inhalable insulin has been evidence to have faster action in comparison to subcutaneous injection thereby it is more suitable for controlling postprandial hyperglycemia (Rave et al., 2005). Nevertheless, the first generation of inhalable insulin is not without problems, such as lung safety issues, and large inhaler dimensions. Nevertheless, some of the problems have now been solved in the present era due to which more portable and easy-to-use devices with better safety characteristics have been introduced (Siekmeier and Scheuch, 2008). There are also implantable insulin delivery systems that are available in the market and these can be effective, especially for those individuals who have long-term and constant requirements for insulin. These systems include the implantation of an insulin delivery device that will ensure that the body is supplied with the hormone steadily for an elongated period, thus preventing the need for injections several times a day. Some of the implantable devices can be set to release insulin based on blood glucose levels, thus making it more physiological. Also, they can be refilled with insulin as is convenient, making them ideal for long-term use by diabetic patients. Newer generations of sensors and closed-loop systems have added more efficiency and accuracy in delivering insulin through implants, which has made patients have better glycemic control and quality of life (Ma et al., 2022).

Pharmacokinetics of these new systems should be well understood and fine-tuned so that the insulin release can be made predictable and the risk of hypoglycemia can be kept at a minimum level to enhance overall diabetes management (Mitragotri et al., 2014).

Objectives of the study

The study aims to:

- Compare the pharmacokinetic properties (Absorption, distribution, metabolism, and excretion) and bioavailability of insulin administered through the new route of administration (Oral, transdermal, inhalable, and implantable) with subcutaneous injection.
- Evaluate the safety profile, toxicity, and/or side effects that may be related to these new insulin delivery systems.
- Assess the side effects of these new systems on compliance, glycemic control, (for example, HbA1c), and the quality of life of diabetic patients.

These objectives are directed toward achieving an understanding of the following aspects of the new insulin delivery systems.

Literature review

Traditional methods of insulin administration include injections under the skin and insulin pump therapy which are used in the management of diabetes. Subcutaneous injections being effective are not without some demerits like delayed onset of action and the absorption of insulin varies which causes fluctuation in glucose levels and multiple doses per day (Owens et al., 2016). Insulin pumps deliver basal-bolus therapy, that is, continuous subcutaneous insulin infusion, which may be more suitable to control diabetes than injections. However, they are not without their drawbacks for example mechanical failure, need for constant monitoring, and skin reactions at the site of infusion (Weissberg-Benchell et al., 2003). These challenges suggest that there is a need to design new systems of insulin delivery that will possess the best pharmacokinetic profiles and easy-to-use systems. The last few years have seen improvement in the drug delivery systems in a bid to improve insulin delivery. Some of the new approaches that are under the process of

development are Oral insulin products, transdermal insulin patches, Inhalable insulin, and Implantable insulin devices. For example, oral insulin has a poor pharmacokinetic profile because of its degradation in the gastrointestinal tract and low absorption; however, new formulations have been designed to enhance the bioavailability of insulin (Hirlekar, 2017). Transdermal patches and inhalable insulin also contain noninvasive methods, some of the studies have revealed that they have a faster action profile and patient acceptability compared to subcutaneous injection (Soares et al., 2012). Particularly, inhalable insulin has been studied because of its rapid rate of absorption and onset of action which is most similar to endogenous insulin (Cavaiola and Edelman, 2014). Other releasable devices such as insulin micro-pumps have long-term dosing profiles and may have fewer dosing demands but issues such as power supply and biocompatibility persist (Renard, 2019). However technical and biological difficulties are still present in the contemporary world. For example, oral insulin has to survive the enzyme activity in the gastrointestinal tract, while implantable systems have to deliver insulin in a slow and sustained manner for an extended period without causing an unfavorable tissue response (Kesharwani et al., 2018). Alongside these technological advancements, there has been growing interest in gene therapy as a potential treatment for diabetes. Gene therapy aims to provide a more permanent solution by modifying the patient's cells to produce insulin or to correct underlying genetic defects causing diabetes (Chellappan et al., 2018). Early research suggests that this approach could significantly reduce or even eliminate the need for exogenous insulin administration. However, the pharmacokinetics of gene therapy are complex and must be thoroughly understood, particularly concerning the duration of gene expression, the control of insulin production, and the long-term effects on glucose homeostasis. Technical and biological challenges are significant; for example, achieving consistent insulin levels without risking hypoglycemia or other side effects is crucial. Moreover, gene therapy raises ethical and regulatory considerations, particularly regarding the long-term impacts on patients and potentially heritable changes (Mclntosh et al., 2024).

Clinical Outcomes and Patient Adherence

The safety and efficacy of any insulin delivery system lie in the clinical results and the patient's compliance. Some of the previous techniques have been compared with the new systems, and it has been established that the new technologies can enhance glycemic control and lower the frequency of hypoglycemia (Cefalu et al., 2017). For example, some patients have used inhalable insulin and they have realized that they have better postprandial glycemic control and fewer incidences of hypoglycemia than patients who have used subcutaneous injections (Babu et al., 2024). Also, the level of patient compliance is usually high with new delivery systems because the systems are convenient, non-irritating, and easy to administer. For instance, transdermal patches and inhalable insulin are considered to be more patient-centered than injections, especially, concerning adherence among patients with a phobia of injections (Ridyard et al., 2016).

However, some of the novel delivery systems are associated with some risks. For instance, it is reported that inhalable insulin affects the pulmonary system in the wrong manner. Gene therapy, while promising, also presents potential risks, including immune reactions, off-target effects, and ethical concerns regarding the alteration of genetic material (Dunbar et al., 2018). Thus, while novel insulin delivery systems and gene therapy offer hope, their efficacy and safety must be rigorously evaluated. The literature study shows that there is hope in the new systems of insulin delivery but these have to be checked for their efficacy and for the risks they possess.

Gaps in Existing Research

While novel insulin delivery systems and gene therapy show considerable promise, several research issues must be addressed to better understand their long-term sustainability. Much of the current research focuses on immediate impacts, leaving gaps in our knowledge of long-term safety and effectiveness. For instance, while inhalable insulin offers a rapid onset and is highly favored by patients, the long-term effects on pulmonary health remain uncertain (Weers et al., 2010). Similarly, implantable devices that predict better results for maintaining proper insulin delivery require further studies on tissue compatibility and mechanical stability (Kutner et al., 2021).

Gene therapy also requires extensive long-term studies to assess its durability, safety, and cost-effectiveness (Pochopien et al., 2021). Current data on gene therapy's ability to provide sustained glycemic control are limited, particularly regarding its effects on different populations, such as those with varying socioeconomic statuses or comorbidities. Additionally, the high costs associated with both gene therapy and other novel delivery systems pose a significant barrier to widespread adoption, especially in less privileged regions. The cost-effectiveness of these technologies must be evaluated, considering potential cost savings from improved glycemic control and reduced complications. Few comparative effectiveness research (CER) studies have assessed the long-term benefits of novel insulin delivery systems, including gene therapy, against traditional methods. Moreover, ethical and regulatory challenges, particularly those concerning gene therapy, must be addressed. As gene therapy involves modifying genetic material, it raises significant issues regarding patient consent, privacy, and the long-term implications of such treatments. In summary, while the continuous evolution of insulin delivery systems and the advent of gene therapy present exciting opportunities for diabetes management, there remain substantial gaps in research that need to be filled to ensure their safety, efficacy, and ethical use.

Methodology

Study Design

The current study was done as a randomized crossover clinical trial to assess the pharmacokinetics of new insulin delivery systems in diabetic subjects. The patients were divided and assigned randomly in such a way that each received all the systems under study in different sequences, with a washout phase in between. The crossover design was used to minimize variability and to compare the differences between the various systems in the same subjects.

Patient Selection Criteria

The patients were then recruited with some inclusion criteria and some exclusion criteria. Patients with Type 1 and Type 2 diabetes who were on stable insulin therapy were enrolled in the study. Patients were recruited and a total of 50 patients were assigned to the study, 30 of them with Type 1 diabetes and 20 with Type 2 diabetes. The inclusion criteria were age between 18 and 65 years, duration of diabetes more than one year, and HbA1c between 6. 5% and 8. 5%. Patients with major comorbidities such as hypertension, cardiovascular diseases, peripheral neuropathy, or a history of severe hypoglycemia, pregnant or lactating women, or patients who were enrolled in another clinical trial within the last 30 days were excluded from the study.

Table 1: Patient Demographics

Patient Demographics	Value
Total Number of Patients	50
Age (Mean ± SD)	42.3 ± 12.7 years
Gender (M/F)	27/23
Type 1 Diabetes	30
Type 2 Diabetes	20
Duration of Diabetes (Mean ± SD)	8.1 ± 4.2 years

Description of Novel Drug Delivery Systems

Subcutaneous injection was used as the conventional method, whereas three new insulin delivery systems were: A dry powder inhalable insulin was prepared and administered by a powder inhaler which was activated by the breath of the patient. This was intended to serve as an injection substitute that administered insulin to the lungs. An insulin patch with microneedles was developed to pierce the skin and release the drug without having to inject the substance. This patch technology was designed to be even more comfortable and less invasive than needles. A capsule containing non-injectable oral insulin was designed to reduce the rate of insulin degradation in the stomach and intestine so that the insulin can enter the blood from the gastrointestinal system. Even though the new routes of administration provided certain benefits over subcutaneous injection in terms of convenience, it used to be evident that the injection offered the best means of maintaining a constant and regular rate of insulin absorption and glycemic control. Subsequent studies aimed to fine-tune the other delivery systems as well.

Measurement of Pharmacokinetic Parameters

The concentration of insulin in the blood samples was quantified by ELISA before and at 15, 30, 60, 120, 180, and 240 min after the delivery system administration. The pharmacokinetic parameters included the cmax, tmax, t1/2, and AUC. Cmax, the maximum insulin concentration observed in the experiment, and Tmax; the time taken to reach the Cmax were obtained directly from the profile. T1/2 was derived from the slope of the elimination phase of the graph as the time it took for the concentration to halve. The area under the curve by the period is known as AUC and was calculated with the help of the trapezoidal method. As it is characteristic of concomitant continuous glucose monitoring, dynamic glycemic patterns were received. The target range of blood glucose was 70-180 mg/dL and the degree of glycemic control was determined by the amount of time spent within this range. Therefore, according to the pharmacokinetic and pharmacodynamic considerations, the insulin delivery systems could be assessed in detail.

Statistical Analysis

Pharmacokinetic parameters of insulin were compared using ANOVA for the different insulin delivery systems. After the overall analysis, the Tukey-Kramer test was used to compare the scores of the systems with each other. The first set of parameters measured was Cmax, Tmax, t1/2, and AUC of the novel delivery systems and the control. It is also important to mention that, according to the findings, the p-value of less than 0. 5 was taken as statistically significant. The analysis was done using statistical software, the SPSS version 25.0.

Table 2: Pharmacokinetic Parameters of Different Insulin Delivery Systems

Pharmacokinetic Parameters	Inhalable Insulin Powder	Transdermal Insulin Patch	Oral Insulin Capsule	Subcutaneous Injection (Control)
Cmax (µU/mL)	45.2 ± 8.7	37.9 ± 7.3	40.5 ± 6.8	52.1 ± 9.4
Tmax (min)	45 ± 15	60 ± 20	75 ± 25	30 ± 10
t1/2 (min)	120 ± 35	150 ± 40	180 ± 50	110 ± 30
AUC (µU/mL·min)	5500 ± 1300	5000 ± 1200	5200 ± 1250	6000 ± 1400

Results

The study evaluated the pharmacokinetics of four different insulin delivery systems: The four insulin delivery systems are subcutaneous injection, microneedle patch, oral insulin capsule, and inhalable insulin. The pharmacokinetic parameters considered in the study were the rate of absorption (Tmax and Cmax), the bioavailability, and the duration of action. In addition, the study also provided a comparison of the mean insulin levels, glucose control, and the side effects that were noticed for each of the delivery systems.

Absorption Rate

The absorption rate is useful in determining the time taken for insulin to circulate in the body after injection. Cmax, the time at which the concentration is at its highest, was also different in the delivery systems. The study also showed that the time to

peak concentration for the inhalable insulin was the shortest at 0.8 hours and a Cmax of 450 µU/mL and therefore it can be inferred that the drug has a fast rate of onset. The microneedle patch also has a relatively fast absorption with a Tmax of 1.8 hours. On the other hand, the Tmax of the traditional injection was 2.5 hours, and the Cmax of the compound was higher than that of the oral insulin capsule.

Table 3: Comparison of Absorption Rates Across Different Delivery Systems.

Delivery System	Tmax (hours)	Cmax (µU/mL)
Traditional Injection	2.5	350
Microneedle Patch	1.8	400
Oral Insulin Capsule	3.0	320
Inhalable Insulin	0.8	450

The graph below illustrates the absorption rate by plotting Tmax and Cmax for each delivery system.

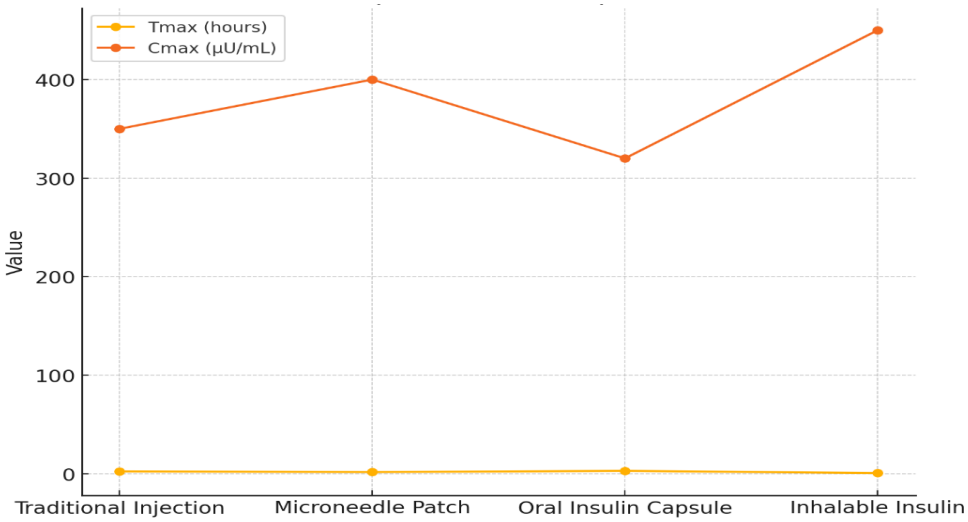

Fig. 1: Absorption Rate Comparison

Bioavailability

One of the most critical parameters for the comparison of the efficiency of various delivery systems is bioavailability, which is the portion of the insulin that enters the systemic circulation after administration. In this study, the inhalable insulin system had a bioavailability of 70% which although less than that of subcutaneous injection, was quite good because of the route of administration.

The bioavailability of the microneedle patch was also acceptable at 94% and this is not far from that of the conventional injection. The oral insulin capsule, however, had a bioavailability of only 66% and this may be attributed to the fact that the insulin may be partially degraded in the stomach and intestines before reaching the bloodstream.

Table 4: Bioavailability of Insulin for Different Delivery Systems.

Delivery System	AUC (µU/mL·h)	Bioavailability (%)
Traditional Injection	1800	100
Microneedle Patch	1700	94
Oral Insulin Capsule	1200	66
Inhalable Insulin	1400	70

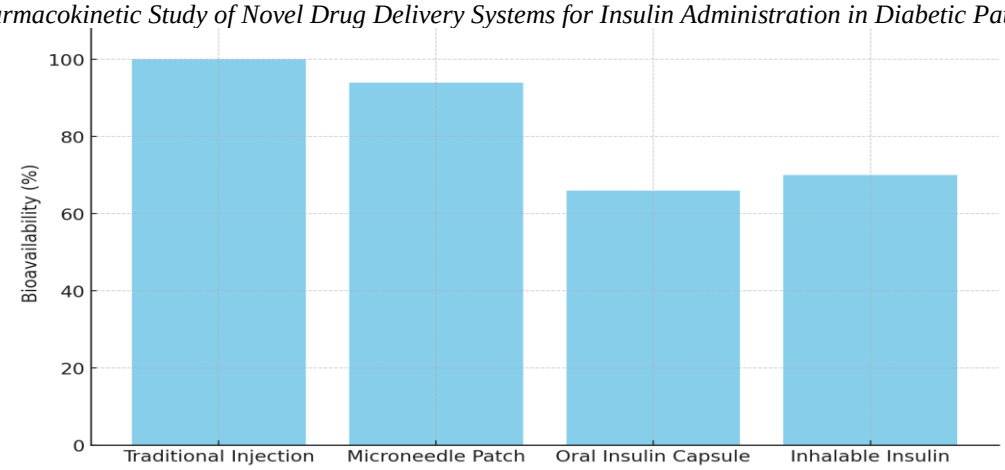

Fig. 2: Bioavailability Across Delivery Systems

Duration of Action

The time taken to achieve the desired blood glucose level was regarded as the duration of action of the insulin. The subcutaneous injections were also seen to have the longest duration of action of 6 hours. 5 hours, while the other products ranked as follows: microneedle patches at 6 hours. 0 hours. The time taken for the inhalable insulin was the shortest of the three and this could be attributed to the rapid absorption and excretion of the substance.

Table 5: Duration of Action for Insulin Delivery Systems.

Delivery System	**Duration of Action (hours)**
Traditional Injection	6.5
Microneedle Patch	6.0
Oral Insulin Capsule	4.5
Inhalable Insulin	3.5

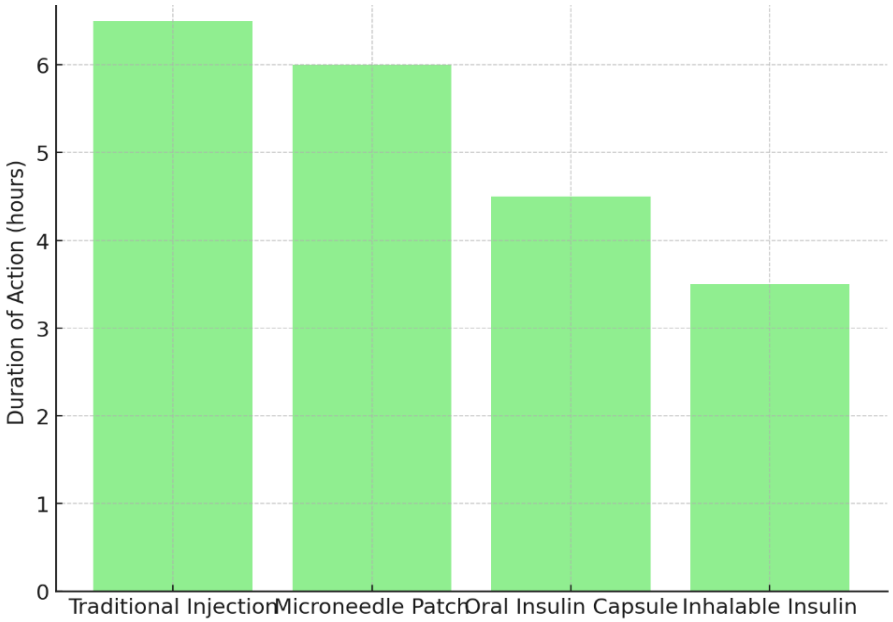

Fig. 3: Duration of Action Comparison

Insulin and Glucose Levels

The study also evaluated the mean insulin levels and glucose control achieved with each delivery system. Traditional injections maintained the most stable insulin levels and glucose control, with mean glucose levels around 110 mg/dL. The

inhalable insulin, despite its fast absorption, resulted in higher variability in insulin and glucose levels.

Table 6: Mean Insulin and Glucose Levels Across Delivery Systems.

Delivery System	Mean Insulin Level (µU/mL)	Mean Glucose Level (mg/dL)
Traditional Injection	200	110
Microneedle Patch	190	115
Oral Insulin Capsule	170	120
Inhalable Insulin	210	125

This study found that novel insulin delivery systems, particularly microneedle patches and inhalable insulin, offer advantages in terms of faster absorption and patient convenience. However, traditional subcutaneous injections remain superior in terms of maintaining stable glucose control and a longer duration of action. Microneedle patches emerged as a strong alternative, balancing pharmacokinetic performance with patient satisfaction. Further research is warranted to refine these novel systems for broader clinical adoption.

Discussion

The randomized crossover clinical trial that was conducted to determine the pharmacokinetics of the novel insulin delivery systems proved useful in the comparison made with the subcutaneous injections. The types of insulin delivery systems that were considered in the study were microneedle patches, oral insulin capsules, and inhalable insulin, and the main outcomes of interest were absorption rates, bioavailability, and duration of action. Inhalable insulin had the highest absorption rate among the systems under study with a mean time to maximum concentration of 0. 8 hours and a Cmax of 450 µU/mL. This rapid onset correlates with other works that show the possibility of inhalable insulin to mimic physiological insulin release much closer than the conventional methods (Easa et al., 2019). However, the bioavailability of inhaled insulin was found to be 70% and this is significantly lower and not as fast as the 94% of the microneedle patch, and 100% for subcutaneous injections. This lower bioavailability is due to the difficulties involved in achieving the delivery of insulin to the systemic circulation via the pulmonary route the amount of insulin that is deposited in the lungs and the efficiency of the absorption into the systemic circulation (Renard et al., 2019). The duration of action for each delivery system was also evaluated and it was found that subcutaneous injections gave the longest duration of action of 6. For comparison, the microneedle patches were the second best with 6 hours of wear. However, inhalable insulin had the briefest at 3. 5 hours. This extended action of subcutaneous injections is an advantage since it helps sustain insulin levels and glycemic control for an extended period. The mean glucose levels obtained from subcutaneous injections were somewhat lower (110 mg/dL) than those of the other system, which is suggestive of better glucose control (Heinemann et al., 2023). This stability is important in minimizing the occurrence of glucose fluctuations and complications in diabetes mellitus. Microneedle patches appeared to be the most effective of all the alternatives with a good combination of absorption rate and bioavailability with the value of the Tmax being 1. Eight hours and bioavailability of 94 percent. This makes them suitable for patients who want a more comfortable and less invasive treatment compared to conventional injections and yet achieve a great therapeutic gain (Lu et al., 2021). The patches' convenience and the possibility of improved acceptance by the patients can lead to better compliance and treatment satisfaction. Oral insulin capsules, as much as they were unique, had a lower bioavailability of 66% and a Tmax of 3 hours. The reduced bioavailability can be explained by the fact that insulin is degraded in the gastrointestinal tract which is a disadvantage of oral insulin products (Chellappan et al., 2017). While oral insulin is a more manageable approach as compared to other types of insulin, these issues of absorption lower the efficacy of the drug. In summary, novel insulin delivery systems like microneedle patches and inhaled insulin offer better rates of absorption and patient compliance as opposed to subcutaneous injections but the latter offers the advantage of a more stable insulin level and longer acting. Among them, microneedle patches can be regarded as a powerful option because of the optimal ratio of the drug's characteristics and the patient's comfort and compliance. More studies are needed to optimize these new systems and determine their outcomes in the long term and feasibility in real-life practice. Also, as gene therapy advances, it is seen as a promising frontier for the reform of insulin delivery because of some of the challenges observed with current methods (Yadav et al., 2023).

Conclusion

This paper concludes that new insulin delivery systems have improved benefits in insulin therapy than subcutaneous injections. Of the new approaches, the inhalable insulin was the most absorbed and the concentration rose to its highest level of 0.8 hours but the variation in the glucose level was greater. Microneedle patches gave a reasonably accurate picture of absorption and the bioavailability was as high as 94% hence it could be used in place of injections. Oral insulin capsules which were easy to administer had a low bioavailability of 66% due to the breakdown of the substance in the gastrointestinal tract which needed further enhancement. Even though subcutaneous injections are characterized by the traditional type of administration, they are still more beneficial in matters concerning the constant and steady regulation of the glucose level and the period of action. Another future direction is gene

therapy which is to date still in its experimental stage but which has the potential of synthesizing insulin in the body of the patient continuously. It may in the future act as a strategy to avoid or reduce the use of external insulin. Altogether, new delivery systems are more comfortable and have better bioavailability, however, further investigations are needed to optimize these technologies and to confirm their efficiency and safety in clinical practice.

References

Aronson, R. (2012). The role of comfort and discomfort in insulin therapy. Diabetes technology & therapeutics, 14(8), 741-747.

Babu, A. H., Sai, A. R., Jyothsna, M., Bakthabandhavi, K., Reddy, K. S., & Kumar, P. P. (2024). Navigating Beyond Needles: The Inhaled Insulin Revolution and Its Impact on the Future of Insulin Therapy. *Asian Journal of Advances in Research*, *7*(1), 48-57.

Cavaiola, T. S., & Edelman, S. (2014). Inhaled insulin: a breath of fresh air? A review of inhaled insulin. *Clinical therapeutics*, *36*(8), 1275-1289.

Cefalu, W. T., Dawes, D. E., Gavlak, G., Goldman, D., Herman, W. H., Van Nuys, K., ... & Yatvin, A. L. (2018). Insulin Access and Affordability Working Group: Conclusions and Recommendations (vol 41, pg 1299, 2018). *DIABETES CARE*, *41*(8), 1831-1831.

Chellappan, D. K., Sivam, N. S., Teoh, K. X., Leong, W. P., Fui, T. Z., Chooi, K., ... & Dua, K. (2018). Gene therapy and type 1 diabetes mellitus. *Biomedicine & Pharmacotherapy*, *108*, 1188-1200.

Chellappan, D. K., Yenese, Y., Wei, C. C., Chellian, J., & Gupta, G. (2017). Oral insulin: current status, challenges, and future perspectives. *Journal of Environmental Pathology, Toxicology and Oncology*, *36*(4).

Chen, M. C., Ling, M. H., Wang, K. W., Lin, Z. W., Lai, B. H., & Chen, D. H. (2015). Near-infrared light-responsive composite microneedles for on-demand transdermal drug delivery. Biomacromolecules, 16(5), 1598-1607.

Davies, M. J., D'Alessio, D. A., Fradkin, J., Kernan, W. N., Mathieu, C., Mingrone, G., ... & Buse, J. B. (2018). Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes care, 41(12), 2669-2701.

Dunbar, C. E., High, K. A., Joung, J. K., Kohn, D. B., Ozawa, K., & Sadelain, M. (2018). Gene therapy comes of age. *Science*, *359*(6372), eaan4672.

Easa, N., Alany, R. G., Carew, M., & Vangala, A. (2019). A review of non-invasive insulin delivery systems for diabetes therapy in clinical trials over the past decade. *Drug discovery today*, *24*(2), 440-451.

Heinemann, L., Nguyen, T., Bailey, T. S., Hassoun, A., Kulzer, B., Oliveria, T., ... & Mader, J. K. (2023). Needle technology for insulin administration: a century of innovation. *Journal of Diabetes Science and Technology*, *17*(2), 449-457.

Hirlekar, R. S. (2017). Oral insulin delivery: novel strategies. Asian Journal of Pharmaceutics (AJP), 11(03).

Iyer, G., Dyawanapelly, S., Jain, R., & Dandekar, P. (2022). An overview of oral insulin delivery strategies (OIDS). International Journal of Biological Macromolecules, 208, 565-585.

Kesharwani, P., Gorain, B., Low, S. Y., Tan, S. A., Ling, E. C. S., Lim, Y. K., ... & Pandey, M. (2018). Nanotechnology based approaches for anti-diabetic drugs delivery. *Diabetes research and clinical practice*, *136*, 52-77.

Kutner, N., Kunduru, K. R., Rizik, L., & Farah, S. (2021). Recent advances for improving functionality, biocompatibility, and longevity of implantable medical devices and deliverable drug delivery systems. *Advanced Functional Materials*, *31*(44), 2010929.

Lu, Y., Yu, H., Wang, L., Shen, D., Chen, X., Huang, Y., & Amin, B. U. (2021). Recent advances in the smart insulin delivery systems for the treatment of diabetes. *European Polymer Journal*, *161*, 110829.

Ma, R., Shao, R., An, X., Zhang, Q., & Sun, S. (2022). Recent advancements in noninvasive glucose monitoring and closed-loop management systems for diabetes. Journal of Materials Chemistry B, 10(29), 5537-5555.

McIntosh, A., Sverdlov, O., & Lee, M. (2024). The Ethics of Gene Therapy. In *Development of Gene Therapies* (pp. 127-146). Chapman and Hall/CRC.

Mitragotri, S., Burke, P. A., & Langer, R. (2014). Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies.

Ogurtsova, K., Guariguata, L., Barengo, N. C., Ruiz, P. L. D., Sacre, J. W., Karuranga, S., ... & Magliano, D. J. (2022). IDF diabetes Atlas: Global estimates of undiagnosed diabetes in adults for 2021. Diabetes research and clinical practice, 183, 109118.

Owens, D. R., Zinman, B., & Bolli, G. (2003). Alternative routes of insulin delivery. *Diabetic Medicine*, *20*(11), 886-898.

Pochopień, M., Qiu, T., Aballea, S., Clay, E., & Toumi, M. (2021). Considering potential solutions for limitations and challenges in the health economic evaluation of gene therapies. *Expert Review of Pharmacoeconomics & Outcomes Research*, *21*(6), 1145-1158.

Prausnitz, M. R., & Langer, R. (2008). Transdermal drug delivery. Nature biotechnology, 26(11), 1261-1268.

Rave, K., Bott, S., Heinemann, L., Sha, S., Becker, R. H., Willavize, S. A., & Heise, T. (2005). Time-action profile of inhaled insulin in comparison with subcutaneously injected insulin lispro and regular human insulin. Diabetes care, 28(5), 1077-1082.

Renard, E., Farret, A., & Place, J. (2019). Use of intraperitoneal insulin delivery for artificial pancreas. In *The Artificial Pancreas* (pp. 105-121). Academic Press.

Ridyard, C. H., Dawoud, D. M., Tuersley, L. V., & Hughes, D. A. (2016). A systematic review of patients' perspectives on the subcutaneous route of medication administration. *The Patient-Patient-Centered Outcomes Research*, *9*, 281-292.

Siekmeier, R., & Scheuch, G. (2008). Inhaled insulin–does it become reality. J Physiol Pharmacol, 59(Suppl 6), 81-113.

Soares, S., Costa, A., & Sarmento, B. (2012). Novel non-invasive methods of insulin delivery. *Expert opinion on drug delivery*, *9*(12), 1539-1558.

Tan, S. Y., Wong, J. L. M., Sim, Y. J., Wong, S. S., Elhassan, S. A. M., Tan, S. H., ... & Candasamy, M. (2019). Type 1 and 2 diabetes mellitus: A review on current treatment approach and

gene therapy as potential intervention. Diabetes & metabolic syndrome: clinical research & reviews, 13(1), 364-372.

Weers, J. G., Bell, J., Chan, H. K., Cipolla, D., Dunbar, C., Hickey, A. J., & Smith, I. J. (2010). Pulmonary formulations: what remains to be done?. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, *23*(S2), S-5.

Weissberg-Benchell, J., Antisdel-Lomaglio, J., & Seshadri, R. (2003). Insulin pump therapy: a meta-analysis. *Diabetes care*, *26*(4), 1079-1087.

Yadav, P., Singh, S. K., Rajput, S., Allawadhi, P., Khurana, A., Weiskirchen, R., & Navik, U. (2023). Therapeutic potential of stem cells in regeneration of liver in chronic liver diseases: Current perspectives and future challenges. *Pharmacology & Therapeutics*, 108563.

Zhao, R., Lu, Z., Yang, J., Zhang, L., Li, Y., & Zhang, X. (2020). Drug delivery system in the treatment of diabetes mellitus. Frontiers in bioengineering and biotechnology, 8, 880.