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A Review on Nano-Particle Based Transdermal Delivery of Anti-Diabetic drugs

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ABSTRACT:

Diabetes mellitus is a concern of disorder globally and which is increasing continuously. Diabetic complications lead to physical, mental and societal issues to patients. Oral medications are being prescribed but these have problems like frequent dosing, side effects and non-patient compliance. Insulin therapy is also problematic due to injectable route of delivery. Dose missing of these treatments lead to fluctuations in blood glucose levels which cause severe adverse effects. Recent developments have shown the potential of transdermal drug administration in association with nanoformulations for improving the efficacy and safety of anti-diabetic medications. Nanotechnology offers modification of size and surface characteristics of nanocarriers which enhances the drug permeation through biological barriers. Transdermal drug delivery in conjunction with nanocarriers provide enhanced permeation, improved bioavailability and sustained effect with reduction in adverse effects. This article first presents the current scenarios of diabetes mellitus and important aspects of transdermal drug delivery systems. In later sections, a detailed description (pharmaceutical and preclinical characteristics) of various nanoformulation assisted transdermal drug delivery systems (polymeric nanoparticles, ethosomes, nanostructured lipid carriers, solid lipid nanoparticles, microemulsions, liposomes, niosomes, nanoemulsions, transethosomes and transfersomes) have been reviewed. Transdermal drug delivery in conjunction with nanoformulations can be utilized for the better management and control of diabetes.

Keywords: Transdermal drug delivery Anti-diabetic Nanoformulations Liposomes Nanoparticles Ethosomes.

Introduction:

The chronic illness known as diabetes mellitus is characterised by an elevated blood glucose level. The body's insufficient supply of insulin causes the blood sugar level to rise. If left untreated, diabetes mellitus can cause mortality, heart failure, and brain stroke. It is more common to have type 2 diabetes than type 1 diabetes, which affects roughly 5–10% of the population. According to estimates from the International Diabetes Federation, 425 million people worldwide suffer with diabetes mellitus. As to the most recent data provided by the World Health Organisation (WHO), the prevalence of diabetes mellitus has increased to 4.7%. By 2030, diabetes is predicted by the WHO to rank as the seventh leading cause of death globally. Insulin usage is now essential for the treatment of diabetes. The loss of beta cells, which produce insulin, leads to a total lack of insulin secretion and is the cause of type 1 diabetes. Type 1A happens when the immune system destroys beta cells. Idiopathic diabetes, commonly referred to as Type 1B diabetes mellitus, is a disorder in which the loss of beta cells is caused by an autoimmune process that is not understood. Compared to type 1, type 2 diabetes mellitus is more strongly correlated with genes and family history. It also depends on environmental conditions. The hallmark of gestational diabetes mellitus is decreased insulin synthesis during pregnancy, which raises blood sugar levels. Diabetic retinopathy is one of the most common conditions affecting the retinal microvasculature in people with diabetes. This medical ailment, commonly known as diabetic eye disease, arises when retinal damage is caused by diabetes mellitus. An additional consequence of diabetes mellitus called diabetic cardiomyopathy is marked by aberrant ventricular functioning.

New therapy approaches have been discovered recently to control diabetes and its consequences. Commonly used anti-diabetic medications include insulin, insulin analogues, and pharmacological candidates that are hypoglycemic but do not include insulin. A potent medication called insulin, a protein molecule, is utilised in clinical settings to treat individuals with diabetes mellitus. The issues related to the distribution of anti-diabetic drugs are still not adequately addressed by the formulation techniques used today. The primary concern pertains to the drug candidates' limited oral bioavailability and instability in the gastrointestinal tract (GIT) as a result of the GIT's harsh environment and reduced water solubility. To address the problems with oral bioavailability, a number of nanoformulation techniques have been developed, including liposomes, nanocrystals, nanosuspensions, polymeric nanoparticles, self-nanoemulsifying drug delivery systems, nanoemulsions, solid lipid nanoparticles, and nanostructured lipid carriers. Numerous transdermal medication delivery systems mediated by nanocarriers have been studied recently to improve diabetes treatment strategies even more. First, the key elements of transdermal drug delivery systems are outlined in this overview. The following section provides a detailed explanation of nanoformulation-based strategies for transdermal drug delivery systems of anti-diabetic medications based on preclinical and pharmaceutical data.

Transdermal drug delivery systems :

Utilizing a variety of transdermal systems, a number of methods and strategies (such as nanoformulations, iontophoresis, electroporation, and

microneedles) are being used to control diabetes. Because these trans-dermal systems escape first pass metabolism and have a delayed drug release feature, they have a higher bioavailability than oral delivery. Furthermore, blood glucose levels can be maintained for a long time due to the controlled and prolonged release of drugs, which enhances patient compliance. Transdermal drug delivery systems aim to administer a specific dosage of medication to patients through their skin and into their bloodstreams. Transdermal drug delivery devices cannot function if the medications do not swiftly penetrate the skin and reach the intended location. The transdermal route, which permits insulin to cross the skin barrier, is the most effective means of delivery. When a patient is unable to swallow pills, has constipation, or is asleep, transdermal distribution is the most effective way to provide medication since it increases patient compliance and bioavailability. Drug-loaded nanoparticles are transferred via the skin when using a transdermal method. For transdermal distribution, the ideal drug candidates should have a low molecular weight (less than 500 Dalton), a skin permeability coefficient of >0.5, a skin permeability rate of 10^{-3} cm/h, a high partiality coefficient (>1), and a non-irritating surface.

Nanoformulation based transdermal delivery systems of anti-diabetic drugs :

Transdermal drug delivery methods aided by nanotechnology have many advantageous qualities, including targeted drug delivery, increased skin penetration, higher bioavailability, and controlled release. Long-acting diabetes treatments can be created by developing an appropriate nanocarrierbased formulation. The subsequent sections provide a summary and discussion of the distinct preclinical and pharmaceutical features of many nanoformulation based transdermal drug delivery systems.

Polymeric nanoparticles

The diameters of polymeric nanoparticles (NPs) range from 10 to 1000 nm, and they can contain active ingredients that are either surface-adsorbed onto the polymeric core or entrapped within it. The terms "nanoparticle" and "Nano sphere," which have different morphologies, are interchangeable. Nano capsules are vesicular structures that function as drug reservoirs and have a polymeric shell enclosing the active medicinal components. Drug molecules are adsorbed at the surface of the sphere or trapped in the interior of solid polymeric nanospheres.27 Behin et al. created Glipizide transdermal films with varying chitosan concentrations (0.5–2.5% w/v). Betacyclodextrin was not included in the formulation of Glipizide used as a control. Moreover, Glipizide was efficiently absorbed into the rats' skin with a precisely regulated drug release when 1.5% w/v chitosan was used. Chitosan 1.5% w/v had the maximum drug concentration and generated a drug release of 96% over the course of a day. It was demonstrated that there was no chance of skin irritation from the formulation. Gliclazide based matrix-type transdermal formulation was created by Jaimini et al. utilising polyethylene glycol 400 as a plasticizer. Moreover, i; e [polymer 2% (w/v), Eudragit1 S100, and PVP in a 2:1 ratio] yielded the best outcomes in comparison to other formulations. Additionally, it was found that the formulation with a 40% w/w plasticizer concentration was adequate to maintain the formulation's integrity and keep it bonded to the medium. 92.77% of the medication was contained in the enhanced formulation, which also provided 87% of the maximum drug release for up to 20 hours. Zhang et al. coated polydopamine/lauric acid (PDA/LA)-coated polymeric microneedles with Metformin. More PDA/LA-coated and Metformin-loaded microneedles were encased in poly(vinylpyrrolidone) (PVP) needles. When Metformin-based microneedles were inserted into skin tissue in diabetic rats, it was found to have a significant anti-diabetic impact. Comparing the microneedle of responsive medication to subcutaneous injection of Metformin, the bioavailability of the former was 95.8± 2.7%.

Ethosomes

Phospholipid nanovesicles called ethersomes are used to deliver active medicinal substances topically and transdermally.31 Bodade et al. used ethanol and dipalmitoyl phosphatidylcholine to create Repaglinide-based ethosomes. When applied to excised rat skin, Repaglinide-based ethosomes had a maximum penetration of 64–97% of the injected dose and measured between 0.171 and 1.727 µm in size. Research on the Repaglinide ethosomal system in vivo demonstrated the drug's prolonged release and antidiabetic efficacy. Glimepiride-based ethosomes were created by Tiwari et al. using varying concentrations of propylene glycol (10% w/w), soy lecithin (3.5–4% w/w), and alcohol (20–30% w/w). The ideal formulation's vesicle range, as determined by an in vitro investigation, was 22–105 nm. The optimised formulation's entrapment efficiency ranged from 47.91 ± 0.3 to 58.4 ±0.3. At the end of the 24-hour period, the cumulative percentage of the optimised formulation ranged from 34.34 ±0.01% to 49.01 ±0.03%, respectively. After 24 hours, the optimised formulation's medication penetration (release) through the egg membrane was 49.01±0.03% and 47.03±0.02%. The optimised ethosomes remained stable at normal temperature (25±2^{0}C) and under refrigeration (4±2 ^{0}C), according to stability experiments.

Wahid et al. used different amounts of ethanol, soy lecithin, and cholesterol to create ethosomes based on saxagliptin. Entrapment effectiveness was 64±1.5329%, polydispersity index was 0.230±0.010, and the vesicle range of the optimised formulation was 117.3± 1.0577 nm during the investigation. Further in vitro research utilising a Franz diffusion cell (area: 3.14 cm^2) was conducted on rat skin to investigate the effects of ethosomal gel and found that it penetrated more drug than ordinary gel. Saxagliptin's developed formulation was discovered to be non-toxic and demonstrated an effective transdermal drug delivery method for saxagliptin via skin. Aouta et al. employed a 3^2factorial design to optimise the ethosomal formulation of a transdermal patch containing a combination of duloxetine and glimepiride, which was produced via a solvent casting technique. Entrapment efficiency and particle size were chosen as dependent variables, while ethanol and phospholipid were used to construct a total of nine formulations. Formulation F9 was shown to be the best option, showing skin permeability of more than 200 µg/cm^2 and in vitro cumulative drug release of more than 60% in 24 hours.

The outcomes demonstrated a promising strategy for the treatment of diabetes and diabetic neuropathic pain using ethosomes integrated into transdermal patches for dual medication delivery.

Nanostructured lipid carriers

Novel pharmaceutical formulations known as nanostructured lipid carriers (NLC) consist of co-surfactants, surfactants, and physiological and biocompatible lipids. Over time, nanostructured lipid carriers a second-generation lipid nanocarrier have emerged as a competitive substitute for first-generation nanoparticles. A nanostructured lipid carrier based on Pioglitazone was developed by Sohrab et al. The optimised nanostructured lipid carrier had a mean size of 166.05 nm, a drug loading capacity of 10.41% with a flux of 47.36 µg/cm^2/h, and an entrapment effectiveness of around 70% for Pioglitazone. In contrast to the commercial formulation (Piosys tablet), Pioglitazone nanostructured lipid carrier based transdermal device was found to lower elevated blood sugar levels in a sustained and long-lasting manner during an in vivo pharmacokinetic trial. Kesharwani et al. developed a nanostructured lipid carrier based Repaglinide that consumes lecithin, oleic acid, cetyl alcohol, and tween 80 in a different study. Significant particle size of the nanostructured lipid carrier during the in vitro investigation was 15.8 nm, with an entrapment efficiency of around 79.82%. Particle size and entrapment efficiency of the solid lipid nanoparticles were 238.4±48.2 nm, and 72.04±1.03%, respectively. The formulation based on nanostructured lipid carriers was shown to be stable after 180 days of storage, according to a stability analysis. The in vivo study verified that the blood sugar level had decreased and that the average blood sugar value was significantly lower than the baseline glucose value at all time intervals.

Jahan et al. used Tween20 and lipid (glyceryl monostearate Lauroglycol™) to create Gliclazide based on a nanostructured lipid carrier. The nanostructured lipid carrier-based Gliclazide was optimised to produce particles with a size of 120.4 nm, a polydispersity index of 0.316, a zeta potential of 5.58 mV, and an entrapment efficiency of 87.32%. Furthermore, during the in vitro study, it was confirmed that, in comparison to standard gel, which is 45.65 2.79%, the drug release of Gliclazide nanostructured lipid carrier was 68.27±2.98%, conventional Gliclazide dispersion was 45.87±2.85%, and Gliclazide nanostructured lipid carrier gel formulation permeation was 76.89±2.52%. Rat skin treated with nanostructured lipid carrier-based gel showed deeper permeation (35 µm) than normal gel (15 µm) according to confocal laser scanning microscopy.

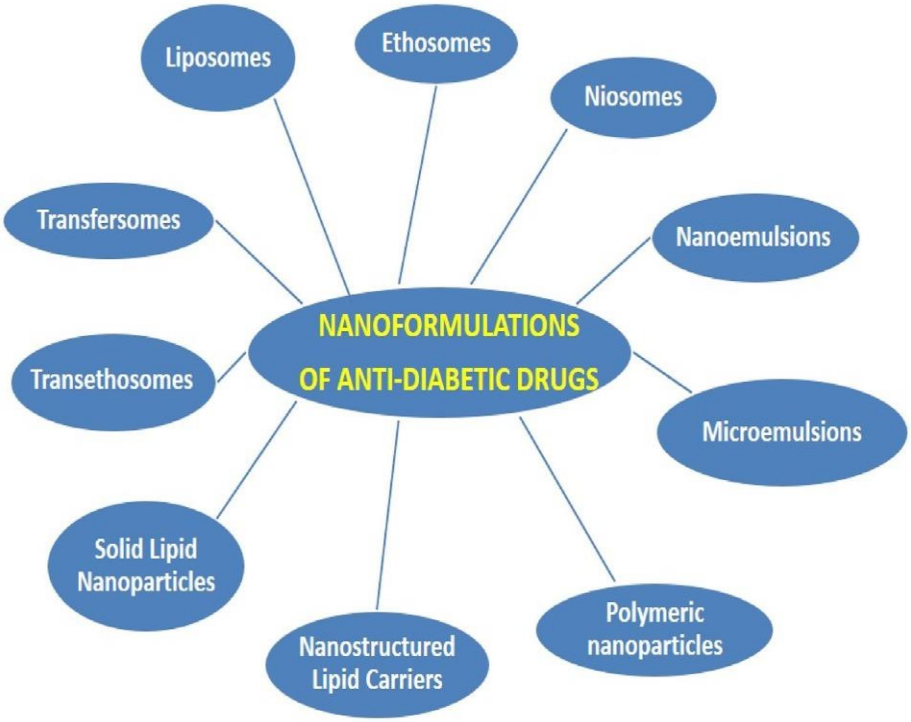

Fig.1.Nanoformulation based approaches of anti- diabetic drugs

Tabel1

Summary of transdermally delivered nanoformulations for diabetes.

Type of nanoformulation	Name of the Drug	Method of Preparation	Major Outcomes	Reference
Polymeric nanoparticles	Glipizide	Stirring followed by sonication	Chitosan with 1.5% (w/v) showed a sustained drug release of ~96% for 24 h and exhibited safety to rat's skin (no irritation reaction).	28
Polymeric nanoparticles	Gliclazide	Solvent casting method	The optimized formulation showed a sustained release of drug (~87%) of up to 20 h and exhibited Korsmeyer-Peppas release kinetics.	29
Polymeric nanoparticles	Metformin	Diffusion method	The bioavailability of optimized formulation delivered transdermally was found to be higher when compared to subcutaneous injection of metformin	30
Ethosomes	Repaglinide	Cold Method	The ethosomal gel formulation of repaglinide showed efficient transdermal drug delivery, sustained drug's effect with reduction in dosing frequency.	32
Ethosomes	Glimepiride	Cold method	The optimized ethosomal formulation showed drug permeation of ~49% after 24 h and was found to be stable at temperatures of 4 ± 2 °C and 25 ± 2 °C.	33
Ethosomes	Saxagliptin	Cold method	The results exhibited the potential of ethosomal formulation for transdermal drug delivery (~51.98 μg/cm^2/h) and found to be safe.	34
Ethosomes	Glimepiride and duloxetine	Cold method	Combined drug loaded ethosomal formulation exhibited the potential for transdermal drug delivery and can be an alternative for the therapy of diabetic neuropathic pain and diabetes.	35
Nanostructured lipid carriers	Pioglitazone	High pressure homogenization	The *in vivo* results exhibited showed 2.17 times bioavailability and lowered blood sugar concentration in a sustained manner for a prolonged duration of time from NLC based formulation in comparison to marketed tablet formulation.	37
Nanostructured lipid carriers	Repaglinide	Solvent diffusion method	The optimized formulation showed particle size of ~157.8 nm and was found to be stable for storage period of 180 days and reduced blood sugar level significantly.	38
Nanostructured lipid carriers	Gliclazide	Melt emulsification followed by ultrasonication	CLSM images of rat's skin applied with NLC based gel exhibited a deeper penetration (35 μm) when compared to the conventional gel formulation (15 μm).	39
Solid lipid nanoparticles	Metformin	Solvent diffusion method	The drug loaded SLNs showed stability as indicated by zeta potential of +27 mV and revealed high drug permeation through Wistar rats' skin.	41
Solid lipid nanoparticles	Repaglinide	Hot homogenization method	The developed drug loaded SLN exhibited particle size in between 85 and 120 nm and the blood glucose levels in rats were decreased and it was sustained for 48 h.	42
Solid lipid nanoparticles	Glibenclamide	Emulsification followed by ultrasonication	The formulation showed stability at 4 °C and *in vivo* studies in rats showed a substantial decrease in blood glucose levels in diabetic rats with fast onset of action (0.5 h) and long duration of anti-diabetic activity (24 h).	44
Microemulsion	Glipizide	Aqueous titration method	The optimized formulation exhibited mean droplet size of ~138 nm and *in vivo* results showed significant blood glucose reduction in Wistar rats when compared to drug alone.	46
Microemulsion	Repaglinide	Aqueous titration method	The developed microemulsion showed skin permeation of 229.19 μg/cm^2 after 24 h, which was 2.30-fold higher in comparison to repaglinide suspension.	47
Microemulsion	Glimepiride	Aqueous titration method	*In vivo* pharmacokinetic results revealed that the bioavailability of glimepiride loaded microemulsion gel was found to be 5.4 times more in comparison to oral drug suspension.	48
Microemulsion	Insulin	Specific emulsification technique	The developed MEIs exhibited potential for the delivery of insulin in therapeutic amounts for prolonged duration of time and showed stability at 4 °C as well as at room temperature.	49
Liposomes	Glipizide and metformin,	Microfluidics manufacturing process	The microfluidics process demonstrated liposomal vesicle size in between 90 and 300 nm. Co-drug-loaded formulation exhibited improved drug release characteristics when compared to single drug formulations.	51
Liposomes	Glipizide	Solvent casting technique	Transdermal film containing drug loaded liposomes showed promising pharmacokinetic profile when compared to oral glipizide and showed enhanced hypoglycaemic effect.	52
Liposomes	Glimepiride	Phase evaporation/melting	Optimized drug loaded liposomal formulation showed encapsulation efficiency of 41.9% and size of 0.51 μm and transdermal films consisting of drug loaded liposomes exhibited elongation ratio of 75%, drug release of 26.8% after 12 h, and folding endurance of 700-fold.	53
Niosomes	Glimepiride	Thin film hydration	*In vivo* studies revealed the superiority of glimepiride niosomes in reducing blood sugar level for a longer duration of time in comparison to free drug and marketed drug product.	55
Niosomes	Pioglitazone	Thin film hydration	The transdermal improvement from proniosomal formulation was 3.16-times more than that of pioglitazone from conventional formulation which was further established by CLSM results.	56
Niosomes	Metformin	Thin film hydration	Drug loaded niosomes exhibited encapsulation in between 13 and 32%, biphasic release pattern. In diabetic rats, metformin loaded niosomal gel applied every 2 days exhibited an improved sustained anti-diabetic activity than oral doses administered daily.	57
Niosomes	Insulin	Thin film hydration	The optimized formulation showed an enhancement in transdermal flux (10-fold) of insulin from niosomal emulgel than the control formulation and *in vivo* results further demonstrated significant reduction in blood glucose levels from niosomal emulgel formulation.	58
Nanoemulsion	Repaglinide	Aqueous titration method	The optimized repaglinide nanoemulsion showed improved hypoglycaemic activity in diabetic rats when compared to tablet formulation.	60
Nanoemulsion	Glimepiride	Spontaneous emulsification	Glimepiride nanoemulsion with clove oil showed improved *in vitro* skin permeation and enhanced hypoglycaemic effect in comparison to pure glimepiride and marketed formulation.	61
Nanoemulsion	Insulin	Aqueous titration method	The in *vivo* results exhibited the slow absorption of insulin through skin of Albino Wistar rats from the nanoemulsion when compared to subcutaneous injection and showed a relative bioavailability of 244.5%.	62

Solid lipid nanoparticles :

Solid lipid nanoparticles (SLN) are usually spherical in shape and range in size from 10 to 1000 nm. Lipid core surfactants are used for stabilization, and the lipid core matrix of solid lipid nanoparticles has the capacity to dissolve lipophilic compounds. For parenteral administration, the emulsifier used is more limited and depends on the delivery method. Sharma et al. used soy lecithin as a lipid foundation, polymethacrylic acid as a polymer, and propylene glycol as a solvent to manufacture Metformin solid lipid nanoparticles, which they then integrated into Methocel™ K100M transdermal patches. The ex vivo permeation study revealed that solid lipid nanoparticles containing a high cumulative dosage of the medication could pass through the skin of Wistar rats. The zeta potential of the optimal formulation was 27 mV. Through the use of electron microscopy, a distinct, spherical structure free from aggregation is shown. During a histological investigation, the transdermal patch contained solid lipid nanoparticles that slightly raised an inflammatory response. The possibility of developing transdermal Metformin for human usage is supported by the study.

Using lipids, such as Cephalin and Lecithin, and Tween 80 as a stabiliser, Vijayan et al. created solid lipid-based Repaglinide nanoparticles. The optimised solid lipid-based formulation was spherical in shape and ranged from 85 to 120 nm, with zeta potential values between - 27.1 ±2.5 and 36.1 ±2.1, as observed by electron microscopy. 80.4 ±4.2% was the entrapment efficiency value while 92.3 ±7.2% was the drug loading capacity. Additionally, it was confirmed via in vivo release trials in diabetic rats that the rats' blood sugar levels were lowered and that these reductions were maintained for more than 48 hours.

Transdermal Metformin patches consisting of HPMC polyvinyl alcohol were developed by Jahan et al., and the rate of Metformin release was tested at 32^0C at different pH levels, i.e., pH 5.4, pH 7.4, and pH 8. The investigation demonstrated that the drug was released from the patches in accordance with the Higuchi diffusion-controlled release pattern. The maximal release rate and kinetic constant were determined at neutral pH, while the kinetic constant and absorption rate were roughly similar between pH 5.4 and pH 8. Transdermal patches for Metformin composed of HPMC polyvinyl alcohol can release the drug over a relatively long period of time because during analysis, the kinetic kinetics of these patches remained affected by pH, and the highest concentration of the medication was accumulated at neutral pH. Using emulsification and ultra sonication procedures, Elbahwy et al. created Glibenclamide based SLNs. Solubility tests were used to identify the optimal lipids. A physicochemical analysis demonstrated the drug's amorphous form, nanoscale size, and pharmacophore preservation. Extended drug release was achieved. from SLN in contrast to medication discontinuation. When the optimised drug-loaded SLNs were tested on diabetic rats, the results demonstrated a significant drop in blood glucose levels with a short half-life (0.5 h) and extended half-life (24 h). The formulation was found to be stable at 4^0C according to the stability data. Overall, Glibenclamide subcutaneous injections treated diabetic rats demonstrated that their diabetes was under control.

Microemulsions

Microemulsions are thermodynamically stable, isotropically transparent distributions with very low interfacial tension between two non-miscible liquids, such water and oil. They are stabilised by a coating of surfactant molecules on the surface. They are stabilised by an interfacial layer of surfactant molecules. Using the water titration approach, Singh et al. created a Glipizide-based microemulsion. Oleic acid was employed as an oil phase, tween-80 was used as a surfactant, and propylene glycol was used as a co-surfactant. The improved micro-emulsion formulation produced an o/w type emulsion with a 138 4.5 nm mean droplet size. The glucose content of the sample was measured with a glucose meter while Wistar rats were being used in in vivo investigations. The outcomes showed that the optimised microemulsion systems were appropriate delivery solutions for Glipizide applied topically. The inclusion complex dramatically lowered blood glucose when compared to the drug taken by itself.

Repaglinide-based microemulsion was created by Shinde et al. utilizing a number of oils, cosurfactants, and surfactants. The microemulsion was optimised with a globule size of 36.15 x 9.89 nm. In comparison to Repaglinide-based microemulsion gel, the steady-state flow for microemulsion-based Repaglinide was found to be approximately 0.5 during ex vivo permeability testing. Following a 24-hour break, the cumulative drug permeation of the microemulsion was found to be 229.19 µg/cm^2, and the microemulsion gel was found to be 180.84 µg/cm^2, or 17.40 µg/cm^2. Furthermore, an oral glucose tolerance test conducted during an in vivo investigation on Sprague Dawley rats revealed that topical application of a Repaglinide-based microemulsion gel significantly reduced the rats' blood glucose levels when compared to oral administration of the same microemulsion. Following a 24-hour break, the cumulative drug permeation of the microemulsion was found to be 229.19 µg/cm^2, and the microemulsion gel was found to be 180.84 µg/cm^2, or 17.40 µg/cm^2. Furthermore, an oral glucose tolerance test conducted during an in vivo investigation on Sprague Dawley rats revealed that topical application of a Repaglinide-based microemulsion gel significantly reduced the rats' blood glucose levels when compared to oral administration of the same microemulsion.

Islam and colleagues developed an ionic liquid-in-oil microemulsion system. insulin formulation (MEI) intended for transdermal administration of insulin. By rupturing the inflexible structure of skin lipids, MEIs which contained biocompatible choline-fatty acids as surfactants were found to effectively boost the penetration of insulin through the skin. Compared to subcutaneous injection (half-life of 1.32 h), the MEIs dramatically reduced blood glucose levels and delivered sustained insulin levels (half-life more than 24 h) in diabetic mouse studies. For three months, the MEIs demonstrated stability at room temperature, and for four months, the biological activity of the MEIs was maintained at 4^0C. The authors came to the conclusion that this strategy might be used for various protein and peptide delivery applications in addition to insulin therapy.

Liposomes

Liposomes are aqueous, bilayer entities composed of phospholipids. Because they have an aqueous core and a lipid bilayer, they can carry both hydrophilic and hydrophobic medicines. Liposomal delivery systems not only increase the solubility of pharmaceuticals but also prevent chemical and biological deterioration of the medications during storage. Joshi et al. used a microfluidics-based manufacturing method to successfully entrap hydrophilic and lipophilic medications (Glipizide and Metformin, respectively) into liposomes. In a single hour, the release rate of Glipizide went from 3% to 12%,

while the release rate of Metformin climbed from 35% to 65%. Medication co-delivery was used to increase the release rates of both drugs. This was explained by the fact that Glipizide alters the density of the lipid packing; it is plausible that this will enhance drug penetration through the lipid bilayer of liposomes. they are extremely curled and small. Moreover, the lipid bilayer is disrupted by the concentration gradient that the aqueous phase of Metformin created across the membrane. Due to both of these factors, the drugs release more quickly and simultaneously, which has a synergistic effect.

The outcomes proved how useful microfluidic technology is for creating liposomal formulations that contain both lipid- and water-soluble medications. Glipizide-based liposomes were created by Mohamed et al. in a different investigation. When compared to the normal formulation, the liposomes with the optimised formulation exhibited greater stability. Glipizide was released continuously during the in vivo investigation, and the rat skin readily allowed for the drug's ex vivo penetration. The pharmacokinetic profile of transdermal film was found to be promising in comparison to the oral Glipizide formulation. Ahmed et al. used process analytical technology and the quality by design concepts to create glimepiride-loaded liposomal films. With a size of 0.51 µm, optimised drug-loaded liposomes demonstrated an encapsulation efficiency of 41.9%. When it was added to transdermal films, it demonstrated a 75% elongation ratio, 26.8% drug release after 12 hours, and a 700-fold folding endurance. The outcomes showed how effective the quality by design method was in creating a glimepiride transdermal film with favourable physicochemical properties for transdermal administration.

Niosomes

Niosomes are self-assembling vesicular drug delivery devices based on cholesterol and non-ionic surfactants. They are bi-layered, having hydrophobic ends facing away from the aqueous solvent and hydrophilic heads pointing in that direction. Owing to their distinct structure, which can be found in the lipid bilayer and aqueous core, respectively, they can absorb both hydrophilic and hydrophobic medications. Glimepiride-loaded Niosomes were created by Mohsen et al. utilizing the thin film hydration technique. Niosomes exhibited a negative charge zeta potential, vesicular size ranging from 186.8 to 797.7 nm, and an encapsulation efficiency of around 98.70%. Compared to the free medication, glimepiride was released from the niosomal formulation in a sustained manner. Further in vivo investigations demonstrated the superiority of drug-loaded niosomes over free drug and commercialized drug products in lowering blood sugar levels and preserving blood drug levels in the therapeutic range for extended periods of time.

Niosomes loaded with Pioglitazone were created by Prasad et al. It was found that the optimised formulation exhibited superior drug delivery capabilities, including better encapsulation, enhanced flux value, and increased penetration of Pioglitazone through the skin. Proniosome remained 3.16 times more active than the control formulation of Pioglitazone (ethanol buffer formulation, 3:7), according to a confocal laser scanning microscopy (CLSM) examination. A pharmacokinetic investigation showed that the niosomal gel based on carbopol had a stronger antidiabetic impact and the highest bioavailability when compared to the commercial formulation. El-Ridy et al. used cholesterol and surfactants to create Metformin-based niosomes. The size of the vesicles was determined to be nanoscale, and the entrapment effectiveness ranged from 13% to 32%. A sustained pattern for the release of Metformin from an optimised niosomal formulation was demonstrated by an in vitro release investigation. When compared to oral therapies administered daily, Metformin loaded niosomal gel applied every two days demonstrated a more robust and effective antidiabetic impact, according to biological observation on diabetic rats.

Insulin-loaded niosomal emulgel was developed by Shehata et al. for transdermal administration. Using paraffin oil, sodium carboxymethyl cellulose, and Tween 80 as independent factors and in vitro drug release, viscosity, and in vitro drug permeation as dependent variables, a 23 full-factorial design was used to optimise the niosomal formulation. Compared to the control formulation of insulin, the optimised formulation demonstrated a 10-fold increase in transdermal flux of niosomal emulgel. According to in vivo data, insulin niosomal emulgel significantly reduced plasma glucose levels (after 6 hours) compared to the control insulin formulation.

Nanoemulsions

Therapeutic drug carriers, or nanoemulsions, are colloidal systems containing droplets with a submicron dimension. Their sizes range from 10 to 1000 nm. Nano-emulsions can include a wide range of actives. On diabetic rats, Akhter et al. prepared an optimised Repaglinide nanoemulsion and administered 1 mg/kg, 2 mg/kg, and 0.5 mg/kg. When compared to the commercial formulation (REGAN®), the Repaglinide-based nanoemulsion demonstrated the highest total medication release of 98.22% and instantaneous medication release within 24 hours. Positive outcomes were observed in in vivo studies using diabetic rats administered at doses of 1 mg/kg, 2 mg/kg, and 0.5 mg/kg of the formulation. Compared with a 64% decrease by the commercial product (2 mg/kg), the blood glucose level reduced by 38%, 67%, and 68%, respectively. The authors concluded that a 1 mg/kg drop in blood glucose levels from the optimised formulation was equivalent to a 2 mg/kg reduction from the commercial formulation. The combination of optimal polydispersity, optimal viscosity, and reduced globule size allowed for faster drug release and enhanced absorption. Glimepiride-based nanoemulsion was created by Razzaq et al. by blending Tween-80, PEG-400, and clove oil. Optimal nanoemulgel formulations were tested in a streptozocin-induced diabetes model, and the results showed that the use of clove oil enhanced both the overall drug penetration through the skin and the antidiabetic efficacy of glimepiride in comparison to the commercial formulation. Using a Simplex lattice architecture,

Ali et al. created an insulin nanoemulsion by varying the independent variables (oleic acid, isopropyl alcohol, tween 80, and water) and the dependent variables (droplet size, flux, and entrapment ratio). The optimised formulation exhibited a flow of 1.75 g/cm2/h, an entrapment ratio of 93.08%, and a droplet size of approximately 41.05 nm. It was discovered that the devised chromatographic insulin detection method was sensitive in the 0.5–2.4 µg/ml range. The three-month stability of the insulin nano-emulsion that was optimised was discovered. Comparing the in vivo results to subcutaneous injection in Albino Wister rats, the delayed penetration of insulin through the skin from the nano-emulsion was seen, with a relative bioavailability of 244.5%. Foeniculum vulgare essential oil-loaded nanoemulsions were created by Mostafa et al. water, Tween 20/propylene glycol, oil phase, and oleic acid. Trans-anethole, the main ingredient of Foeniculum vulgare, has an encapsulation efficiency of 64% in the developed nanoemulsion, according to an HPLC approach. The formulation that was optimised demonstrated small droplet size and thermodynamic stability. When compared to a standard

emulsion, the essential oil-based nanoemulsion demonstrated a better skin penetration performance. A single topical dose of 120 mg/kg for seven days demonstrated the high potential of an essential oil-based nanoemulsion in lowering plasma glucose levels in rats, according to in vivo studies.

Transethosomes

Ethosomes, which are lipid and ethanol-based vesicles, are employed mainly for transdermal drug delivery. Due to some limitations associated with ethosomes, transethosomes are developed containing edge activators such as Span 80, Span 25, Tween 80, and sodium cholate. Transethosomes make the pathways that enable greater penetration into the epidermal layers and enhanced medication delivery. Mishra et al formulated Berberine hydrochloride loaded transethosomes with soya lecithin, phospholipid, oleic acid as an edge activator, and cholesterol. The optimized Berberine hydrochloride loaded transethosomes were inspected for their vesicle size, entrapment effectiveness, loading capacity, polydispersity index, and zeta potential.

Additionally, transmission electron microscopy, differential scanning calorimetric analysis, and powder X-ray diffraction were carried out. The optimised formulation demonstrated appropriate vesicles size (185–435 nm) and zeta potential (17.34–24.35 mV) during in vitro evaluation. The polydispersity index (0.321–0.471) varied between 0.141 and 0.321, and there was high drug entrapment (67.05–85.21%). Transethosomes loaded with Berberine hydrochloride were released for a full day, as per an in vitro drug release research. Deeper skin layers have an accumulation of transethosomes, as shown by confocal laser scanning microscopy. The results of stability testing showed that optimised transethosomes fared better at room temperature (25^0C) than in the refrigerator (4^0C).

Transfersomes

The term "transfersome" describes a class of carrier system whereby at least one inner aqueous compartment the activator of the edge is surrounded by a lipid bilayer. These are liposomes that have been altered to include edge activators. The goal of creating these vesicular networks was to efficiently transfer medications or other therapeutic substances across cellular membranes. Using phosphatidylcholine and sodium deoxycholate, Chauhan et al. created a glimepiride formulation based on transfersomes, which they then turned into protransfersome gel. After conducting a skin permeation examination on pig ear skin for 24 hours using Franz diffusion, it was discovered that the protransfersomal gel's flux value (5.129 ±1.24 µg/cm2/h) was still superior to that of the drug suspension (0.430 µg/cm2/h). For three months, the recipe that was optimised showed improved stability. A pharmacokinetics study showed that protransfersomal glimepiride gel had notable drug release in comparison to a traditional transdermal patch. Pioglitazone-based nanotransfersomes were created by Ramkanth et al., refined using the Box-Behnken design, and then further transformed into gel form. In comparison to drug-loaded oral nanotransfersomal formulations, the optimised nanotransfersomal gel performed better over an extended period of time in monitoring diabetes and hypertension in Wistar rats during pharmacokinetic studies. It was discovered that this kind of combination medicine would work well for treating patients with diabetes who are also hypertensive. Malakar et al. used soy lecithin, cholesterol, Tween 80, and sodium deoxycholate to manufacture an insulin-based transfersome gel. The proposed formulation's drug entrapment efficacy was approximately 56.55%, and the typical vesicles' dimensions ranged from 625 to 815 nm. For 24 hours, the in vitro permeabilization of insulin from optimised transfersomal gel through swine ear skin followed zero-order kinetics. The extended hypoglycemic impact of the optimised transfersomal gel was observed 24 hours after transdermal application in diabetic rats (induced by alloxan). To enhance the qualities of silymarin, Abdallah et al. created a transfersomal gel filled with silymarin. Utilising two dependent variables (encapsulation efficiency and in vitro drug release) and three independent variables (surfactant concentration, phospholipid concentration, and sonication time), a three-factor, three-level Box Behnken design was utilised to optimise the trans-ethosomal formulation. The drug-loaded transferral gel was found to have a pH of 7.05, a spread ability of 55.35 mm, and a viscosity of 6.27 Pa. Transdermal flux of silymarin-loaded transfersomal gel was 92.41 µg/cm2/h, much higher than that of silymarin solution. Comparing silymarin-loaded transfersomal gel to oral silymarin suspension and silymarin gel, in vivo studies showed a significant reduction in blood glucose levels. [66-70]

Conclusion :

Transdermal distribution of drug-loaded nanoformulations has several advantages for managing diabetes, including increased bioavailability, controlled release, non-invasive administration, less side effects, decreased frequency of doses, and better patient compliance. It has been demonstrated that medications could effectively pass the epidermal barrier and be administered into the systemic circulation via nanoemulsions, liposomes, polymeric nanoparticles, ethosomes, etc. Some problems still need to be fixed, including skin permeability, long-term stability, loading capacity, and possible skin irritations. Studies at the molecular level are urgently needed for transdermal administration of antidi- abetic drugs based on nanoformulations, which can be used in clinical settings.

REFERENCES:

1. Zhang Y, Yu J, Kahkoska AR, Wang J, Buse JB, Gu Z. Advances in transdermal insulin delivery. Adv Drug Deliv Rev. 2019;139:51–70.
2. Srinivasan S, Elumalai K, Cherian BV, Ramanujam SK. Formulation and characterization of Metformin hydrochloride orodispersible tablets with super disintegrants. Intelligent Pharm. 2023. https://doi.org/10.1016/j.ipha.2023.06.006.
3. Ng LC, Gupta M. Transdermal drug delivery systems in diabetes management: a review. Asian J Pharm Sci. 2020;15(1):13–25.
4. Singh S, Kushwaha P, Gupta SK. Exploring the potential of traditional herbs in the management of diabetic retinopathy: an overview. Drug Res. 2020;70(7):298–309.
5. Shamim A, Siddiqui HH, Mahmood T, Bagga P, Kumar R. A comprehensive study on literature evidence, clinical studies and practices of herbal drugs for diabetic neuropathy and cardiomyopathy. Asian J Pharm Clin Res. 2017;10(9):30–37.

6. Sabbagh F, Muhamad II, Niazmand R, Dikshit PK, Kim BS. Recent progress in polymeric non-invasive insulin delivery. Int J Biol Macromol. 2022;203:222–243.
7. Sabbagh F, Kim BS. Recent advances in polymeric transdermal drug delivery systems. J Contr Release. 2022;341:132–146.
8. Zhao R, Lu Z, Yang J, Zhang L, Li Y, Zhang X. Drug delivery system in the treatment of diabetes mellitus. Front Bioeng Biotechnol. 2020;8:880.
9. Panwar R, Raghuwanshi N, Srivastava AK, Sharma AK, Pruthi V. In-vivo sustained release of nanoencapsulated ferulic acid and its impact in induced diabetes. Mater Sci Eng C Mater Biol Appl. 2018;92:381–392.
10. Chen X, Ren Y, Feng Y, Xu X, Tan H, Li J. Cp1-11 peptide/insulin complex loaded pH- responsive nanoparticles with enhanced oral bioactivity. Int J Pharm. 2019;562: 23–30.
11. Garg V, Kaur P, Gulati M, et al. Coadministration of polypeptide-k and curcumin through solid self-nanoemulsifying drug delivery system for better therapeutic effect against diabetes mellitus: formulation, optimization, biopharmaceutical characterization, and pharmacodynamic assessment. Assay Drug Dev Technol. 2019; 17(4):201–221.
12. Xu HY, Liu CS, Huang CL, et al. Nanoemulsion improves hypoglycemic efficacy of Berberine by overcoming its gastrointestinal challenge. Colloids Surf B Biointerfaces. 2019;181:927–934.
13. Mohseni R, ArabSadeghabadi Z, Ziamajidi N, Abbasalipourkabir R, RezaeiFarimani A. Oral administration of resveratrol-loaded solid lipid nanoparticle improves insulin resistance through targeting expression of SNARE proteins in adipose and muscle tissue in rats with type 2 diabetes. Nanoscale Res Lett. 2019; 14(1):227.
14. Piazzini V, Micheli L, Luceri C, et al. Nanostructured lipid carriers for oral delivery of silymarin: improving its absorption and in vivo efficacy in type 2 diabetes and metabolic syndrome model. Int J Pharm. 2019;572:118838.
15. Amjadi S, Mesgari Abbasi M, Shokouhi B, Ghorbani M, Hamishehkar H. Enhancement of therapeutic efficacy of betanin for diabetes treatment by liposomal nanocarriers. J Funct Foods. 2019;59:119–128.
16. Suzuki K, Kim KS, Bae YH. Long-term oral administration of Exendin-4 to control type 2 diabetes in a rat model. J Contr Release. 28;294:259-267..
17. Gouda W, Hafiz NA, Mageed L, Alazzouni AS, Khalil WKB, Abdelmaksoud MDE. Effects of nano-curcumin on gene expression of insulin and insulin receptor. Bull Natl Res Cent. 2019;43:128.
18. Zhao X, Wang W, Zu Y, et al. Preparation and characterization of betulin nanoparticles for oral hypoglycemic drug by antisolvent precipitation. Drug Deliv. 2014;21(6):467–479.
19. Mamatha T, Zubair M, Begum S, Muneera T. Various emerging trends in insulin drug delivery systems. Br J Pharmaceut Res. 2015;5(5):294–308.
20. Anhalt H, Bohannon NJ. Insulin patch pump: their development and future in closed- loop systems. Diabetes Technol Ther. 2010;12(s1):5–51.
21. Ali Asad, Ahmad Usama. Nanoemulsion as a vehicle in transdermal drug delivery. Insights Biomed. 2018;3:2572–5610.
22. Rastogi V, Yadav P. Transdermal drug delivery system: an overview. Asian J Pharm. 2014;6(3):16.
23. Alkilani AZ, McCrudden MT, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics. 2015;7(4):438–470.
24. Naik A, Kalia YN, Guy RH. Transdermal drug delivery: overcoming the skin's barrier function. Pharm Sci Technol Today. 2000;3(9):318–326.
25. Keleb E, Sharma RK, Mosa EB, Aljahwi AA. Transdermal drug delivery system design and evaluation. Int J Adv Pharm. 2010;1(3).
26. Shariq M, Mahmood T, Kushwaha P, et al. Fabrication of nanoformulation containing carvedilol and silk protein sericin against doxorubicin induced cardiac damage in rats. Pharmaceuticals. 2023;16:561.
27. Zielin_ska A, Carreiro_ F, Oliveira AM, et al. Polymeric nanoparticles: production, characterization, toxicology and ecotoxicology. Molecules. 2020;25(16):3731.
28. Behin SR, Punitha IS, Saju F. Development of matrix dispersion transdermal therapeutic system containing Glipizide. Der Pharm Lett. 2013;5(3):278– 286.
29. Jaimini M, Tiwari R, Sharma SK, Chauhan BS, Mohan S. Formulation and in-vitro evaluation of transdermal film of Gliclazide for type II diabetes mellitus. Int J Pharm Sci. 2013;4(2):339–343.
30. Zhang Y, Jiang G, Hong W, et al. Polymeric microneedles integrated with Metformin- loaded and PDA/LA-Coated hollow mesoporous SiO2 for NIR-triggered transdermal delivery on diabetic rats. ACS Appl Bio Mater. 2018;1(6):1906–1917.
31. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: an overview. J Adv Pharm Technol Res. 2010;1(3):274–282, 3.
32. Bodade SS, Shaikh KS, Kamble MS, Chaudhari PD. A study on ethosomes as mode for transdermal delivery of an antidiabetic drug. Drug Deliv. 2013;20(1):40–46.
33. Tiwari A, Mishra MK, Shukla A. Formulation and evaluation of anti-diabetic ethosome. Br J Biomed. 2018;2:289–299.
34. Wahid AA, Ravouru N. Development, characterization and in-vitro evaluation of ethosomal gel for transdermal delivery of saxagliptin. J Glob Trends Pharm Sci. 2017; 8(4):4429–4437.
35. Aouta EK, Patra CN. Design, optimization and characterization of combined ethosomal transdermal patch of glimepiride and duloxetine drug regimen for diabetes and associated neuropathic pain management. Curr Drug Ther. 2022;17(5): 359–368.
36. Chauhan I, Yasir M, Verma M, Singh AP. Nanostructured lipid carriers: a ground- breaking approach for transdermal drug delivery. Adv Pharm Bull. 2020:150–165.

37. Sohrab A, Mohammed A, Khan A, et al. Nanostructured lipid carriers of Pioglitazone for transdermal application: from experimental design to bioactivity detail. Drug Deliv. 2016;23(2):601–609.
38. Kesharwani R, Patel D, Yadav PK. Bioavailability enhancement of Repaglinide using nano lipid carrier: preparation characterization and in vivo evaluation. Int J Appl Pharm. 2022;14(5):181–189.
39. Jahan S, Aqil M, Ahad A, et al. Nanostructured lipid carrier for transdermal Gliclazide delivery: development and optimization by box-behnken design. Inorg Nano-Met Chem. 2022;(2):1556–2470.
40. Mehnert W, Mader K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001;47(2–3):165–196.
41. Sharma RK, Sharma N, Rana S, Shivkumar HG. Solid lipid nanoparticles as a carrier of Metformin for transdermal delivery. Int J Drug Deliv. 5(2):137–145..
42. Vijayan V, Jayachandran E, Anburaj J, Rao DS, Vijayan KJK. Transdermal delivery of Repaglinide from solid lipid nanoparticles in diabetic rats: in vitro and in vivo studies. J Pharm Sci Res. 2011;3(3):1077–1081.
43. Jahan L, Ferdaus R, Shaheen SM, Sultan MZ, Mazid MA. In vitro transdermal delivery of Metformin from an HPMC/PVA based TDS-patch at different pH. J Sci Res. 2011; 3(3):651–657.
44. Elbahwy IA, Ibrahim HM, Ismael HR, Kasem AA. Enhancing bioavailability and controlling the release of Glibenclamide from optimized solid lipid nanoparticles. J Drug Deliv Sci Technol. 2017;38:78–89.
45. Vidya S, Sejal V. Formulation and evaluation of microemulsion-based hydrogel for topical delivery. Int J Pharm Investig. 2012;2(3):140–149, 3.
46. Singh MK, Chandel V, Gupta V, Ramteke S. Formulation development and characterization of microemulsion for topical delivery of Glipizide. Der Pharm Lett. 2010;2(3):33–42.
47. Shinde UA, Modani SH, Singh KH. Design and development of Repaglinide microemulsion gel for transdermal delivery. AAPS PharmSciTech. 2018;(1):315–325.
48. Madikattu K, Kalamata VN, Srisailam K. Enhanced bioavailability of glimepiride through microemulsion based transdermal gels. Int J Pharm Sci Res. 2016;7(12): 5052–5055.
49. Islam MR, Uddin S, Chowdhury MR, Wakabayashi R, Moniruzzaman M, Goto M. Insulin transdermal delivery system for diabetes treatment using a biocompatible ionic liquid-based microemulsion. ACS Appl Mater Interfaces. 2021;13(36): 42461–42472.
50. Claudia Z, Sandro M. Pharmaceutical liposomal drug delivery: a review of new delivery systems and a look at the regulatory landscape. Drug Deliv. 2016;9:1–11.
51. Joshi S, Hussain MT, Roces CB, et al. Microfluidics based manufacture of liposomes simultaneously entrapping hydrophilic and lipophilic drugs. Int J Pharm. 2016; 514(1).
52. Mohamed B, Nadia A, Basmah A, Ahlam A, Amal E. Transdermal Glipizide delivery system based on chitosan-coated deformable liposomes: development, ex vivo, and in vivo studies. Pharmaceutics. 2022;14(4):826.
53. Ahmed OAA, Kurakula M, Banjar ZM, Afouna MI, Zidan AS. Quality by design coupled with near infrared in formulation of transdermal glimepiride liposomal films. J Pharm Sci. 2015;104(6):2062–2075.
54. Kazi KM, Mandal AS, Biswas N, et al. Niosome: a future of targeted drug delivery systems. J Adv Pharm Technol Res. 2010;(4):374–380.
55. Mohsen AM, AbouSamra MM, ElShebiney SA. Enhanced oral bioavailability and sustained delivery of glimepiride via niosomal encapsulation: in- vitro characterization and in vivo evaluation. Drug Dev Ind Pharm. 2017;8:1254–1264.
56. Prasad PS, Imam SS, Sultana Y, Ali A. QbD-based Carbopol transgel formulation: characterization, pharmacokinetic assessment and therapeutic efficacy in diabetes. Drug Deliv. 2016;23(3):1057–1066.
57. El-Ridy MS, Yehia SA, El-Sayed I, Younis MM, Rahman RFA, El-Gamil MA. Metformin hydrochloride and wound healing: from nanoformulation to pharmacological evaluation. J Liposome Res. 2019;29(4):343–356.
58. Shehata TM, Nair AB, Al-Dhubiab BE, et al. Vesicular emulgel based system for transdermal delivery of insulin: factorial design and in vivo evaluation. Appl Sci. 2020;10(15):5341.
59. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech. 2015;5(2):123–127.
60. Akhtar J, Siddiqui HH, Fareed S, Badruddeen Khalid M, Aqil M. Nanoemulsion: for improved oral delivery of Repaglinide. Drug Deliv. 2016;23(6):2026–2034.
61. Razzaq FA, Asif M, Asghar S, et al. Glimepiride-loaded nanoemulgel; development, in vitro characterization, ex vivo permeation and in vivo antidiabetic evaluation. Cells. 2021;10(9):2404.
62. Ali FR, Shoaib MH, Ali SA, et al. A nanoemulsion based transdermal delivery of insulin: formulation development, optimization, in-vitro permeation across Strat-M® membrane and its pharmacokinetic/pharmacodynamic evaluation. J Drug Deliv Sci Technol. 2022;71:103338.
63. Mostafa DM, El-Alim SHA, Asfour MH, Al-Okbi SY, Mohamed DA, Awad G. Transdermal nanoemulsions of Foeniculum vulgare mill. Essential oil: preparation,Characterization and evaluation of antidiabetic potential. J Drug Deliv Sci Technol. 2015;29:99–106.
64. Mishra KK, Kaur CD, Verma S, Sahu AK, Dash DK, Kashyap P, Mishra SP. Transethosomes and Nanoethosomes: Recent Approach on Transdermal Drug Delivery System. IntechOpen. . https://doi.org/10.5772/intechopen.81152.
65. Mishra KK, Kaur CD. Development of BBN-hcl loaded transethosomes for enhanced transdermal delivery. Thai J Pharm Sci. 2022;46(2):191–202.
66. Opatha SAT, Titapiwatanakun V, Chutoprapat R. Transfersomes: a promising nanoencapsulation technique for transdermal drug delivery. Pharmaceutics. 2020; 12(9):855.
67. Chauhan MK, Gulati A. Aggrandized transdermal delivery of glimepiride via transfersomes: formulation, evaluation and statistical optimization. J Drug Deliv Ther. 2016;6(4):48–54.

68. Ramkanth S, Anitha P, Gayathri R, Mohan S, Babu D. Formulation and design optimization of nano-transferosomes using Pioglitazone and eprosartan mesylate for concomitant therapy against diabetes and hypertension. Eur J Pharm Sci. 2021;162: 105811.
69. Malakar J, Sen SO, Nayak AK, Sen KK. Formulation, optimization and evaluation of transferosomal gel for transdermal insulin delivery. Saudi Pharm J. 2012;20(4): 355–363.
70. Abdallah MH, Abu Lila AS, Shawky SM, et al. Experimental design and optimization of nano-transfersomal gel to enhance the hypoglycaemic activity of silymarin. Polymers. 2022;14(3):508.
71. Thirunavukkarasu A, Nithya R, Jeyanthi J. Transdermal drug delivery systems for the effective management of type 2 diabetes mellitus. Diabetes Res Clin Pract. 2022;194: 109996.
72. Islam MR, Uddin S, Chowdhury MR, Wakabayashi R, Moniruzzaman M, Goto M. Insulin transdermal delivery system for diabetes treatment using a biocompatible ionic liquid-based microemulsion. ACS Appl Mater Interfaces. 2021;13(36): 42461–42472.