Review Article

Topical Metformin: A Promising Alternative to Alleviate the Gastrointestinal Side Effects Associated with Oral Medication in Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder which is characterized by persistent hyperglycemia. It can be due to an altered insulin secretion, resistance to insulin's peripheral actions, or both. Metformin (dimethylbiguanide), is acknowledged as an essential frontline tool worldwide for the treatment of type 2 diabetes & is the highly prescribed oral hypoglycemic drug. It is the only biguanide derivative available in the market. It is the most affordable & effective medical option to deal with the disease. But there are prevailing & well known side-effects that arise with taking the medicine orally; amongst which the most prevalent are the gastrointestinal side-effects. The common GI side-effects associated with Metformin are diarrhea, constipation, anorexia, indigestion, dyspepsia, nausea, heartburn, vomiting, abdominal pain, bloating, retching, flatulence, etc. Innovations in technologies in development of transdermal drug delivery system for the treatment of diabetes will help in convenient and easy administration of the drug. Hence, in the present review article, we have made an attempt to explore the recent advances in the transdermal drug delivery system and the significant advantages of the novel topical/transdermal use of metformin over oral route of administration in order to lower down the gastrointestinal side-effects associated with the oral administration of the medication.

Keywords: Gastrointestinal side-effects, Metformin, oral, Transdermal, Topical, Type-2 Diabetes Mellitus.

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INTRODUCTION

In 1995, Metformin was introduced in the USA after years of intensive research after the French physician Jean Sterne, first reported the use of metformin to treat diabetes in 1957. Metformin is widely used in the treatment of non-insulin-dependent diabetes mellitus and is highly effective in decreasing the risk of disease development. Metformin is a tried and tested medicine that has been used for decades to treat Type 2 Diabetes Mellitus, and is suggested by most experts as a first-line therapy. It is safe, affordable, effective, and well tolerated by most people. However, unwanted side-effects often come hand in hand with administering metformin orally. The most prevalent side-effects include the gastrointestinal side-effects that are encountered in at least one in three patients prescribed with Metformin, which in turn leads the patients to discontinue or suspend the medicinal treatment altogether (Fig.1).[1] Fortunately, recent developments in topical/transdermal treatment options have offered patients a new way towards receiving the benefits of Metformin without facing the complications that arise after oral administration of the medicine in the treatment of Type 2 Diabetes Mellitus.

According to recent studies, the gastrointestinal system appears to be a key site of action for metformin hydrochloride. However, it is also the site of a prominent metformin drawback like intolerance, which often limits metformin dosing. For the short-term therapy of type 2 diabetes, the medication is prescribed orally in divided multiple doses of 300-500mg[1]. Because of the drug's short half-life, frequent administration is required, which leads to poor patient compliance (4-6hrs). As a consequence, an alternative non-invasive technique of drug administration is required. Transdermal delivery seems to be an appealing mode of administration for regulating Metformin hydrochloride blood levels for a prolonged period. Hence, due to the benefits of that transdermal systems offer over invasive injectable and oral dose forms, they have attracted increased attention and emerged as a viable hope in diabetes control over the last decade.

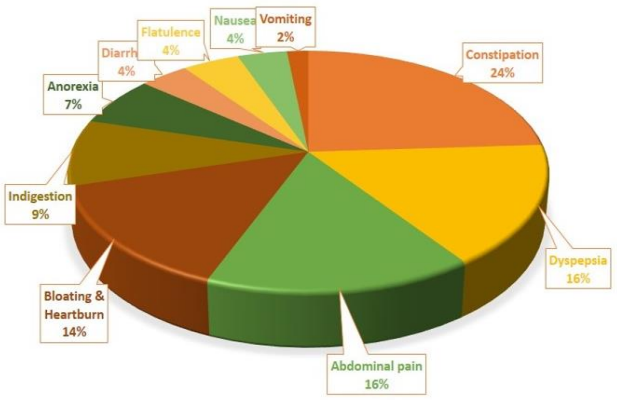

Figure 1: Gastrointestinal side-effects of Metformin (oral)

Transdermal Metformin Therapy (TMT) is a novel drug delivery method that provides the same be hoof of the medication that is obtained after taking the medicine orally, while eliminating or discarding the side-effects often seen with oral administration. Transdermal Metformin Therapy (TMT) is simply the incorporation of Metformin into a topically applicable base such as cream, ointment or gel that can be directly applied onto the skin. The Metformin gets pushed into the body through the skin and enters the systemic circulation/bloodstream. This therapy bypasses the Gastrointestinal tract altogether and avoids the first pass metabolism.

Mechanism of Action of Metformin

Metformin reduces hepatic glucose production & absorption. Treatment with Metformin decreases fasting plasma glucose by 25 to 30 %[2]. Metformin for its access to hepatocytes utilizes AMP Activated Protein Kinase (AMPK)[3], resulting in reduced hepatic production of Glucose & decreasing glucose, utilization of glucose [3, 4].

In liver & skeletal muscle the mitochondrial characteristic & AMPK pursuit have taken into consideration as budding mechanisms & has received a whole lot attention using which Metformin exerts its effects effectively. Metformin improves the lipid profile, in Polycystic Ovarian Syndrome, restores the characteristic of ovaries, & reduces infiltration of fat withinside the liver & lesser microvascular & macrovascular headaches associated to T2DM. Recently, in research Metformin has been observed as an introduction remedy for cancer, as gestational diabetes remedy & restores characteristic of ovaries & in pre-diabetic people for stopping T2DM [5].

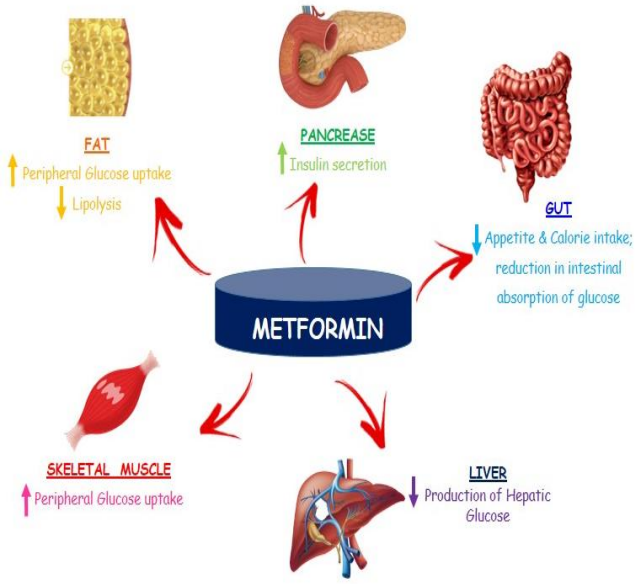

Figure 2: Mechanism of action of Metformin

Within the intestine, enteroendocrine cells discharge Glucagon-Like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Peptide (GIP), which can be taken into thought as pivotal determinants for the transfer of glucose taking after a feast[6].Glucose manufacturing is diminished both through bringing down gluconeogenesis or through glycogenolysis[7,8,9].In spite of the fact that in evaluating the rates of these metabolic forms there are confinements in these studies in terms of strategies utilized[2]. To a lesser extent, the glucose levels within the plasma are brought down by increasing peripheral glucose take-up by the fat tissues and skeletal muscles[9]. (FIG.2)

Gastrointestinal Side – Effects of Metformin:

The mechanism under metformin – induced GI intolerance is not clear. However, there are different assumptions suggested, including stimulation of serotonin secretion in the intestines, changes in incretin, glucose metabolism and Bile salts malabsorption. Metformin structure was discovered to have some similarities with 5-hydroxytrptamine 5- HT3 selective agonists for receptors; transported by Serotonin Reuptake Transporter (SERT).Serotonin release (5-hydroxytrptamine (5-HT)) from the intestine leads to symptoms such as nausea, vomiting and diarrhea (FIG.3).

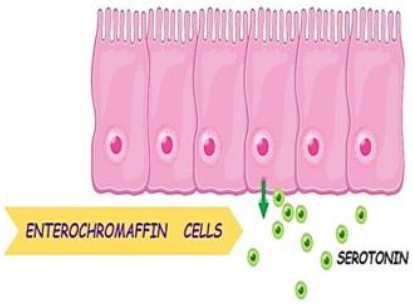

Figure 3: Serotonin release from intestine leads to GI problem

Duodenal biopsy study in subjects inexperienced with metformin it was discovered that metformin stimulates the release of serotonin from Enterochromaffin Cells; however, this effect is not mediated by 5HT3 receptors[14, 15].

Metformin absorption via SERT or Organic Cation Transporter (OCT1) results in reduced serotonin transport and GI side effects. The membrane of enterocytes expresses a number of solute service transporters which are concerned with the absorption of metformin from the intestinal lumen[15]. This contains organic cation transporter (OCT) 1, Plasma Membrane Monoamine Transporter (PMAT), carnitine/cation transporter 1, and OCT3 (FIG.5). The abated metformin transport by way of OCT1 increases the metformin aggregation in the entrails, developing in larger risk of GI prejudice (FIG.4). Metformin increases the bile acid pool in the colon, primarily via reducing ileum absorption. This alteration of enterohepatic bile salts has the potential to affect cholesterol homeostasis, glucose homeostasis, and enteroendocrine function (FIG.6). Changes in the microbiome and stool consistency could potentially contribute to metformin sensitivity[13, 14].

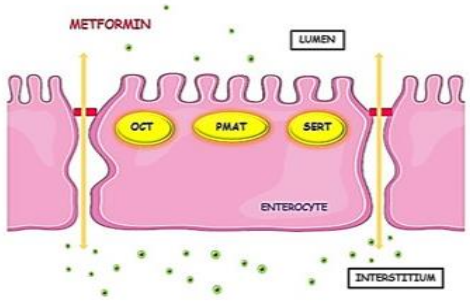

Figure 4: Maximum absorption via OCT1, SERT and PMAT in small intestine increases concentration of Metformin due to reduced transportation causing GI Intolerance.

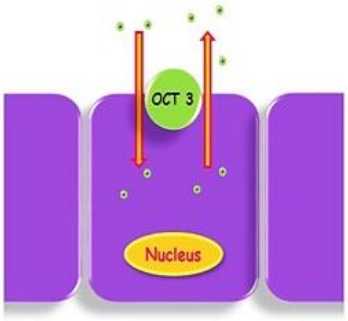

Figure 5: Metformin secretion by salivary gland via OCT3 into saliva leads to Dysgeusia.

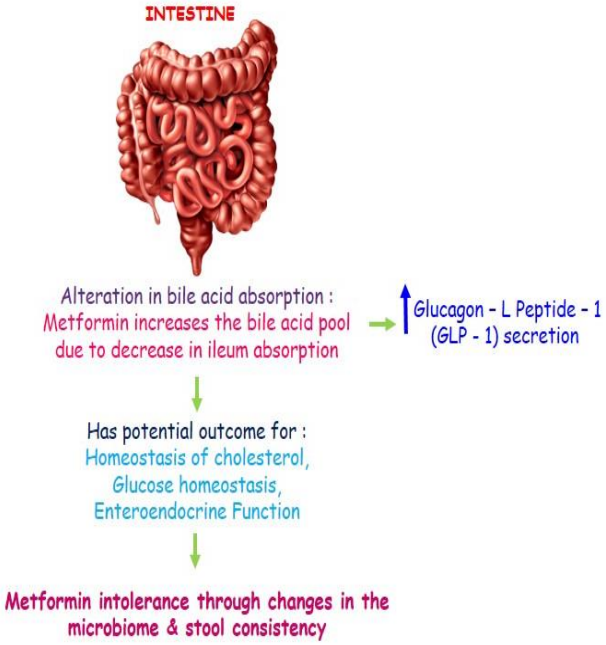

Figure 6: Alteration in the bile acid pool, increase in bile acid concentration, increase GLP secretion

Recent Advancements in the Transdermal Drug Delivery Systems:

In the last few decades the advancement in technology has helped to improve the transdermal delivery of drug thus enabling the delivery of macromolecules through the skin. Different techniques can be applied in order to enhance the penetration of drug and bypass the stratum corneum either by occlusion, by optimizing the formulation or by using physical methods. The most researched physical methods are iontophoresis, sonophoresis, electroporation and microneedles.

A] Physical Methods for Transdermal Drug Delivery

(a) Electrically Assisted Methods:

Iontophoresis

Iontophoresis is the most advanced painless and effective technology accelerating the transport of ionized and unionized moieties across the skin by means of electric current (usually, 500 microamperes cm2)[16,17]. The drug delivery is based on the principle that like charges repel each other. Mechanism of iontophoresis includes diffusion, migration or electro-osmosis [17]. Electro-osmosis is the mass flow of fluid that takes place in the same direction as the flow of counter-ions when a voltage difference is enforced [17]. On implementation of electromotive force the drug repels and moves across the stratum corneum in the direction of the cathode placed elsewhere on the body[18]. Iontophoresis offered rapid method of delivering water soluble and ionized medication into the skin; Reduces the chance of dose variation; Self-administration is possible; Bypasses hepatic first pass effect, higher patient compliance[17].

Sonophoresis

Sonophoresis/Ultrasound/Phonophoresis accelerates the movement of drug across skin using ultrasonic energy [19]. Sonophoresis takes place when the ultrasound waves stimulate micro-vibrations in the pores and skin dermis and surges the kinetic power of molecules. When sound is discharged at a specific frequency, the sound waves disturb the lipid bilayer of Stratum corneum and enhances permeability[19].The sonophoresis offers several merits like avoids hepatic first pass effect, Reduces daily dosing, Substitute to oral administration when the route is unsuitable as in case of vomiting, diarrhea, etc., self-administration possible[19].

Electroporation

Also known as Electropermeabilization is a remarkable increase in the electric conductivity and permeability of the plasma membrane of the cell resulting from an externally applied electric field. The definition of electroporation given by Tsong which is still widely accepted now is that electroporation is the transient loss of semi-permeability of cell membranes subject to the electric pulses, thus leading to "ion leakage, escape of metabolites, and increased uptake by cells of drugs, Molecular probes and DNA"[20]. Short impulses of high voltage current are applied on the skin producing hydrophilic pores in the intercellular bilayers by temporary lipid re-alignment. Electroporation is effective with nearly all cell and species types[21].

(b) Mechanical Method:

Microneedles

Lately advances in bioengineering have brought about the emergence of numerous new "active" enhancement technologies designed to temporarily evade the stratum corneum barrier[22]. Microstructured transdermal devices additionally referred to as microneedle includes hundreds of needles per array of microstructured projections covered with a drug or vaccine ranging in size from 100 microns to 2mm[23]; carried out to the pores and skin to offer intradermal shipping of lively agents, which in any other case might not cross the stratum corneum. The mechanism for delivery, however, isn't always primarily based totally on diffusion. It's primarily based totally on the transient mechanical disruption of the pores and skin and the position of the drug or vaccine in the epidermis where it is easier to get to the action site[24].

B] Optimization of Formulation for Transdermal Drug Delivery

Nanocarriers

Nanocarriers are categorized into colloidal structures with an average of less than 500 nanometres[25]. Emerging Nanocarriers, including liposomes, nanoparticles (NPs), Nano-emulsion, and Micro-emulsion are the most studied for transdermal drug delivery. Lipid-based NPs, including liposomes, solid lipid nanoparticles, niosomes, carriers of nanostructured lipids and Nano-emulsions are widely used for transdermal drug delivery[26].

Solid Lipid Nanoparticles (SLNs)

Gasco & Muller in 1991 discovered Solid Lipid Nanoparticles. SLNs are usually spherical with size ranging between 50 to 1000nm[27]. SLNs are made up of lipids physiologically dispersed in aqueous surfactant solution or water. SLNs were designed with the aim to overpower the demerits associated with liquid state of oil droplets. The lipid nature of SLNs increases their efficiency at trapping and deep penetration into the skin. The choice of surfactant and lipid mixture plays a vital role in lipid nanoparticle drug encapsulation[28]. NPs systems based on lipids may have a thick layer on the surface of the skin with an occlusive effect thus improving the hydration of the skin. The implication of the surfactants present in this system may loosen or fluidise the layer cornea and may improve the permeation of loaded drug[27].

Advantages – Feasible for both hydrophilic and hydrophobic/lipophilic drugs, increases drug stability, enhanced biocompatibility etc[29].

Nanostructured Lipid Carriers (NLCs)

NLC, the second generation of SLNs consists of a binary blend of solid lipids and a spatially different fluid lipid as a hybrid carrier with average size between 10-500 nm[30]. The NLC mixture consists of a long chain of liquid and lipids (oil) with a ratio of 99.9 to 0.1 and a short chain of solids and lipids with ratio 70: 30 [30, 31]. Solid lipid carrier systems that are available in nanometre such as solid lipid nanoparticles (SLN), was introduced as an alternative to liposome. SLN has multiple limitations. Incomplete ability to load medicines and expel medicines through storage, all these limitations can be minimized or removed by the new DDS solid lipids NLCs. New and modified type of NLC's are available having a meticulous nanostructure. These meticulous nanostructures help to improve the stability of the formulations as well as enhance the bioavailability, drug loading etc.[32]. NLC's additionally minimizes the extraordinary troubles which are related to the SLN for a number drugs, troubles like low payload, drug expulsion in the course of storage and SLN's dispersions due to the excessive water content material in it[33-36].NLC is able to transport both lipophilic and hydrophilic drugs at the same time[37]; NLC's help improving stability of pharmaceuticals by facilitating control and targeted drug release[38].

Liposomes

Liposomes are closely related colloidal structures consisting of one or more lipid bilayer spheres holding water compartments[39, 40]. The purpose of any DDS is to modulate the pharmacokinetics and distribution of the drug in a useful way. Among the various systems of administration, liposome applications formulations and products are extremely wide-ranging. Due to its ability to carry wide range of drugs such as Anticancer, Antimalarial, Antifungal drugs, etc.[41]. Advantages – increases efficacy, stability, increased pharmacokinetic effects, facilitates transport of drugs across membranes [42, 43].

Niosomes

Niosomes are monolayer or multilayer spheroidal structures made of surfactants and regarded as the counterpart of liposomes[44]. They can incorporate both hydrophilic and lipophilic moieties. They improve the oral solubility and bioavailability of minimally soluble drugs and also improve skin permeability of drugs when applied by topical method. Niosome shows flexibility in their characteristic structure and can be designed depending upon the desired situation. They can be delivered to the site of action orally, parenterally as well as topically[45].

Nanocrystals

Drug nanocrystals are pure solid drug particles with an average diameter of less than 1000 nm[46]. The term drug nanocrystals implies a crystal state of discrete particles, but depending on the method of production they may also be partially or completely amorphous. Drug nanocrystals are formed by reducing the particle size, resulting in an increase in the solubility of the drug. This technology is therefore being studied to increase the bioavailability of medicines that are not very soluble in water[47]. Nanocrystals are ideal for administration on all routes, enhances solubility and oral bioavailability[47].

Nanoparticles

Nanoparticles are composed of a minimum of 100 atoms. Nanoparticle, is the combined name for the nanosphere

and nanocapsules. Nanoparticles are recognized to be targeted drug administration because of its targeting nature. Nanoparticles are used to dispense DNA, medications, proteins. Due to its nature, size and optical property, it helps the nanoformulation to easily penetrate the physiological barrier and reach the target cell[48]. It can be administered through various routes, it offers targeted delivery of drug, and it increases the resistance time of the drug[49].

Previous Studies on the Transdermal Drug Delivery of Metformin HCl:

Table 1: Work done so far on transdermal delivery of Metformin

Name of author	Year of study	Study carried
Ali Nokhodchi, Jafar Akbari et.al [61]	2018	Developed Topical gel of Solid Lipid Nanoparticle: A hopeful promise as a Dermal Delivery System.
Nitan Bharti Gupta et.al [62]	2012	Formulated and Evaluated Metformin proniosomal gel for the treatment of Diabetes Mellitus.
Ryan F. Donnelly et.al [63]	2018	Formulated and Characterized Hydrogel forming Microneedles for enhancing Transdermal delivery of Metformin.
Ravi Teja Allena et.al [64]	2012	Prepared and Evaluated Transdermal patches of Metformin Hydrochloride using natural polymers for sustained release.

Topical solid lipid nanoparticle gel:

Ali Nokhodchi, Jafar Akbari et.al (2018) performed formulation of Solid Lipid Nanoparticles loaded Topical gel of Metformin with the aim of enhancing dermal delivery of Metformin by using Ultrasonication method[50,51]. It was observed that solid lipid nanoparticles are suitable carrier for skin delivery of metformin. It helped increase the skin delivery of higher concentrations of metformin to the deeper layers of the skin. The study suggested that Solid Lipid Nanoparticle loaded topical gel of Metformin can be a hopeful promise for Dermal Delivery[52].

Proniosomal gel:

Nitan Bharti Gupta et.al (2012) performed study on formulation and evaluation of Metformin Proniosomal Gel for Treatment of Diabetes Mellitus. Metformin hydrochloride was successfully integrated by coacervation phase separation method in proniosomal preparations which prolonged drug delivery. Surfactant used in the proniosomal gel formulation also helped enhance the penetration. Proniosome gels were found to have high capture efficiency and also mediate controlled systemic transdermal delivery of metformin hydrochloride for the treatment of type 2 diabetes. Metformin hydrochloride could be prescribed in low-dose proniosome gels for transdermal administration. This improves bioavailability, protects recipients from high-dose damage[53].

Hydrogel –forming microneedles (MN):

Ryan F. Donnelly et.al (2018) formulated Hydrogel-forming Microneedles to amplify the transdermal delivery of Metformin Hydrochloride. Hydrogel-forming microneedle arrays (MN) were typically formed from the aqueous blends of poly (methylvinylether/maleic acid) and poly (ethylene glycol) with the help of micromoulding process using silicone moulds that were prepared by laser engineering technology[54]. It was found that Hydrogel-forming MN, which itself is drug-free, swells in the skin and diffuses the drug contained in the adhesive reservoir layer into the skin microcirculation for systemic absorption. The study demonstrated the ability of hydrogel-forming MNs to enhance transdermal delivery of a metformin hydrochloride. Hydrogel-forming MN may enable sustained transdermal delivery of metformin HCl, which can minimize gastrointestinal side effects and avoid fluctuations in small intestinal absorption associated with oral routes of administration[54]. Hydrogel-forming microneedles have showcased the ability to enhance the transdermal delivery of many therapeutic substances with a wide range of physicochemical properties. This highlights the versatility of this MNs type and shows that hydrogel-forming MNs have considerable promise for commercial success. When introduced into the skin, hydrogel-forming MN comes into contact with interstitial fluid[55]. MN swells to form a porous aqueous microduct through which the drug substance diffuses and reaches the microcirculation of the skin. The aqueous network produced by these MNs is suitable for Transdermal delivery of relatively water- soluble drugs such as metformin HCl. Thus Hydrogel-forming MNs are clearly a promising technology that could be used to enhance transdermal delivery of a metformin HCL[56].

Transdermal Patch:

Ravi Teja Allena et.al (2012) developed Transdermal Patches of Metformin Hydrochloride for Sustained

release. Transdermal patch is an adhesive patch that is placed on the skin with the intent to deliver a sustained-released dose of medication through the skin to treat systemic illnesses[57]. The first transdermal patch approved in the US by the FDA. Such system provides a variety of significant clinical advantageous over others like tablet and injections. Transdermal patch provides controlled release of the drug into the patient, and enables a steady blood-level profile, leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage form. In addition, the dosage form of transdermal patches is user- friendly, convenient, painless, and offers multi-day dosing, it is generally accepted for delivery of metformin HCL to treat the type 2 diabetics[58].

Transdermal patch are type of drug delivery system which are designed to support the passage of metformin HCL from the upper surface of the skin into the systemic circulation. Permeability of the transdermal drug is primarily affected by the three factors-mobility of the drug within the vehicle, release of drug from the vehicle and permeation[59]. The most tremendous advantage to patients will have a much easier treatment option in which a transdermal patch with predetermined release rate can be applied to the skin. A long-lasting drug release profile also ensures better glucose control and better glucose profile prediction. The prepared transdermal patch showed optimum drug content and sustained drug release. The study reported that application of transdermal patches containing Metformin hydrochloride achieved sustained drug delivery without gastric irritation[59, 60].

CONCLUSION

Since diabetes mellitus is a chronic condition that requires long-term medication, innovation in treatment strategies would be appreciated. Transdermal medication in diabetes management are seen as a promising approach to achieving better clinical outcomes. A higher drug bioavailability may be achieved, and with this, diabetic sufferers will then have a lesser dosing frequency as compared to twice-every day dosing of traditional oral agents and 3 instances or maybe 4 instances every day of insulin injection. Compared to SC insulin injecting, transdermal delivery could help reduce stigma whereby patients must inject themselves with insulin. Overall, this area becomes an effort for researchers to explore and venture in as various transdermal approaches have shown very desirable advantages in improving the bioavailability of medicines, reducing the dosing frequency, and ease of administration resulting in better patient compliance. More dedicated research therefore needs to be done in order to alleviate the gastrointestinal side-effects that come from taking the medication orally.

REFERENCES

1. Harrigan RA, Nathan MS, Beattie P. Oral agents for the treatment of type 2 diabetes mellitus: pharmacology, toxicity, and treatment. ANN Emerg Med 2001; 38:68-78.
2. Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, Shulman GI. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 2000; 49: 2063-2069.
3. Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights? Diabetologia 2013; 56: 1898-1906.
4. Zhou G, Myers R, Li Y, Chen Y, Sheng X, Fenyk-MelodyJ, Musi N. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Investig 2001;108: 1167-1174.
5. Napolitano A, Miller S, Nicholls AW, Baker D, Van Horn S, Thomas E, Nunez DJ. Novel gut-based pharmacology of metformin in patients with type 2 diabetes mellitus.PLoS One 2014; 9: 100778.
6. Drucker DJ. The biology of incretin hormones. Cell Metabol 2006; 3: 153-165.
7. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 1995; 333: 550-554.
8. Cusi K, Consoli A, Defronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metabol 1996; 81: 4059-4067.
9. Christiansen MP, Linfoot PA, Neese RA, Hellerstein M. Metformin effects upon post absorptive intra hepatic carbohydrate fluxes. Sci Info Datab 1997.
10. Yu JG, Kruszynska YT, Mulford MI, Olefsky JM. A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated type 2 diabetic patients. Diabetes 1999; 48: 2414-2421.
11. Wiernsperger NF, Bailey CJ. The antihyperglycaemic effect of metformin. Drugs 1999; 58: 31-39.
12. Hundal RS, Inzucchi SE. Metformin. Drugs 2003; 63:1879-1894
13. Dujic T, Zhou K, Donnelly LA, Tavendale R, Palmer CN, Pearson ER. Association of organic cation transporter 1 with intolerance to metformin in type 2 diabetes: a GoDARTS study. Diabetes 2015; 64: 1786-1793.
14. Cubeddu LX, Bonisch H, Gothert M, Molderings G, Racke K, Ramadori G, Schworer H. Effects of metformin on intestinal 5-hydroxytryptamine (5-HT) release and on 5-HT 3 receptors. Naunyn-Schmiedebergs Arc Pharmacology 2000; 361: 85-91.
15. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. Diabetologia 2016; 59: 426-435.
16. Carter D, Howlett HCS, Wiernsperger NF, Bailey CJ. Differential effects of metformin on bile salt absorption from the jejunum and ileum. Diab Obes Metabol 2003; 5: 120-125.
17. Guy, R. H. (1998). Iontophoresis–recent developments. J. Pharm. Pharmacol. 50,371–374. doi: 10.1111/j.2042-7158.1998.tb06875.x .

18. Guy, R. H., Kalia, Y. N., Delgado-Charro, M. B., Merino, V., López, A., and Marro,D. Iontophoresis: electrorepulsion and electroosmosis. Control.Release 2000;64:129–132. doi: 10.1016/s0168-3659(99)00132-7.
19. Barry, B. W. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur. J. Pharm. Sci. 2001;14:101–114. doi: 10.1016/s0928-0987(01)00167-1.
20. Tsong, T. Y. "Electroporation of cell membranes," in Electroporation and Electrofusion in Cell Biology, eds E. Neumann, A. E. Sowers and C. A. Jordan (Berlin: Springer), 1989; 149–163.
21. Prausnitz, M. R., Bose, V. G., Langer, R., and Weaver, J. C. Electroporation of mammalian skin: a mechanism to enhance transdermal drug delivery. Proc.Natl. Acad. Sci. U.S.A. 1993;90:10504–10508.
22. P. Bora, L. Kumar, A. Bansal, Microneedle Technology for Advanced Drug Delivery: Evolving Vistas, 2008.
23. M.R. Prausnitz, R. Langer, Transdermal drug delivery, Nat. Biotechnol. 2008;26(11):1261–1268.
24. M. Gupta, U. Agrawal, S.P. Vyas, Nanocarrier-based topical drug delivery for the treatment of skin diseases, Expert Opin. Drug Deliv. 2012;9(7):783–804.
25. Neubert, R. H. H. Potentials of new nanocarriers for dermal and transdermal drug delivery. Eur. J. Pharm.Biopharm. 2011;77:1–2.
26. Patzelt, A., Mak, W. C., Jung, S., Knorr, F., Meinke, M. C., Richter, H., et al. Do nanoparticles have a future in dermal drug delivery? J. Control. Release 2017;246:174–182.
27. M.R. Gasco, Method for producing solid lipid microspheres having a narrow size distribution, US Patent 5 250 236 (1993).
28. Ghasemiyeh, P., Azadi, A., Daneshamouz, S., Heidari, R., Azarpira, N., and Mohammadi-Samani, S. Cyproterone acetate-loaded nanostructured lipid carriers: effect of particle size on skin penetration and follicular targeting. Pharm. Dev. Technol. 2019;24:812–823. doi: 10.1080/10837450.2019.1596133.
29. Charcosset C, El-Harati A, Fessi H. Preparation of solid lipid nanoparticles using a membrane contactor. J Control Release 2005;108:112-120.
30. Radtke M, Müller RH. Nanostructured Lipid Carriers: A novel generation of solid lipid drug drug Carriers. Pharmaceutical Technology Europe 1991;17:1-4.
31. Peddinti S. Nanostructured lipid carriers as a drug carrier. J Pharm Nanotechnol Nanostruc 2016;4: 68-74.
32. Jenning V, Schafer-Korting M, Gohla S. Vitamin A-loaded solid lipid nanoparticles for topical use: drug release properties. J Control Release 2000;66: 115-126.
33. Jenning V, Mäder KGS. Solid lipid nanoparticles (SLNTM) based on binary mixtures of liquid and solid lipids: a 1H-NMR study. Pharm 2000;205: 15-21.
34. Jenning V, Gohla S. Comparison of wax and glyceride solid lipid nanoparticles. Int J Pharm Sci 2000;196: 219-222.
35. Uner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspective. Int J Nanomedicine 2007;2: 289-300.
36. Ravichandar R, Jamuna RR, Varadarajan S. Article Study of adverse drug reactions in a tertiary care teaching hospital. IJBCP 2016;5:209-212.
37. Purohit DK, Nandgude TD, Poddar SS. Nano-lipid carriers for topical application: Current scenario. Asian J Pharm 2016;10: 1-9.
38. Chrai SS, Murari R, Ahmad I. Liposomes: A review. Pharm Technol 2002;26:28-34.
39. Kargar M, Moghimipour E, Ramezani Z, Handali S. Application potential of liposomal delivery systems prepared by lipids extracted from E. coli cultures. Annu Res Rev Biol 2014;4:1319.
40. Johnston MJ, Semple SC, Klimuk SK, Ansell S, Maurer N, Cullis PR, et al. Characterization of the drug retention and pharmacokinetic properties of liposomal nanoparticles containing dihydrosphingomyelin. Biochim Biophys Acta 2007;1768:1121-7.
41. Chow TH, Lin YY, Hwang JJ, Wang HE, Tseng YL, Wang SJ, et al. Improvement of biodistribution and therapeutic index via increase of polyethylene glycol on drug-carrying liposomes in an HT-29/luc xenografted mouse model. Anticancer Res 2009;29:2111-20.
42. Lim SB, Banerjee A, Önyüksel H. Improvement of drug safety by the use of lipid-based nanocarriers. Control Release 2012;163:34-45.
43. Balakrishnan, P., Shanmugam, S., Lee, W. S., Lee, W. M., Kim, J. O., Oh, D. H., et al. Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery. Int. J. Pharm. 2009;377:1–8. doi: 10.1016/j.ijpharm.2009.04. 020.
44. Tavano, L., Picci, N., Ioele, G., and Muzzalupo, R. Tetracycline-niosomes versus tetracycline hydrochlo-ride-niosomes: how to modulate encapsulation and percutaneous permeation properties. J. Drug. 2017;1:1–6.
45. Pireddu, R., Caddeo, C., Valenti, D., Marongiu, F., Scano, A., Ennas, G., et al. Diclofenac acid nanocrystals as an effective strategy to reduce in vivo skin inflammation by improving dermal drug bioavailability. Colloids Surf. B 2016;143:64–70.
46. Shegokar, R. "What nanocrystals can offer to cosmetic and dermal formulations," in Nanobiomaterials in Galenic Formulations and Cosmetics, ed. A. Grumezescu (Amsterdam: Elsevier), 2016;69–91.
47. Sovan Lal Pal, Utpal jana, K. Manna, G.P Mohanta, R.Manavalan -Nanoparticles: An overview of preparation and characterization. Journal of applied pharmaceutical science, 2011;1:228-234.
48. Michael J Welch, Craig J Hawker and Karen Wooley, The advantages of nanoparticles for PET.journal of nanoparticles, 2009;50:1743-1746.
49. M. Shah, Y. Agrawal, K. Garala, A. Ramkishan, Solid Lipid Nanoparticles of a water soluble drug, Ciprofloxacin Hydrochloride, Indian J Pharm Sci, 2012;74:434.
50. S.M. Kazemi D, Rostamizadeh K, Zabihian A., Topical gel of Solid Lipid Nanoparticles, A hopeful promise as a dermal delivery system, IJPRI, 2014;7:1-6.
51. R. Kumar, V. Sinha, Curcumin loaded nanostructured lipid carriers for ocular drug delivery: Design, Optimization and Characterization, AAPS PharmSciTech, 2017;18:884-894.

52. Thejaswi C, Rao M, Gobinath M, Radharani J, Hemafaith V, Venugopalaih P, A review on design and characterization of proniosomes as a drug carrier, IJAPN, 2011;1:16-19.

53. R.F. Donnelly, T.R.R. Singh, M.J. Garland, et al., Hydrogel-forming microneedle arrays for enhanced transdermal drug delivery, Adv. Funct. Mater. 2012;22:4879–4890.

54. M.C. Kearney, E.C. Salvador, S.J. Fallows, et al., Microneedle-mediated delivery of donepezil: potential for improved treatment options in Alzheimer's disease, Eur. J. Pharm. Biopharm. 2016;103:43–50.

55. L.J. McCreight, C.J. Bailey, E.R. Pearson, Metformin and the gastrointestinal tract, Diabetologia 2016;59:426–435.

56. Shaheen SM, Jahan L, Ferdaus R. A therapeutic TDS patch of Metformin from a HPMC-PVA blend studied with a biological membrane of fish-swim bladder: an approach for dermal application in NIDDM. PJPS 2015;28(5):1619–24.

57. Arora P. Mukherjee B. Design development of physicochemical in vitro and in vivo evaluation of transdermal patches containing diclofenac diethyl ammonium salt. Indian J. Pharm. Sci. 2002; 91(9): 2076-89.

58. Saxena M, Mutalik S and Reddy MS. Formulation and evaluation of transdermal patches of metoclopramide hydrochloride, Indian Drugs. 2006; 43(9): 740-45.

59. Arora P. Mukherjee B. Design development of physicochemical in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. Indian J. Pharm. Sci. 2002; 91(9): 2076-89.

60. Ali Nokhodchi, Jafar Akbari et al.. Topical gel of Metformin Solid Lipid Nanoparticle: A hopeful promise as a dermal delivery system. Colloids and surface B:Biointerface, 2018;175:150-157.

61. Nitan Bharti Gupta et al., Preparation and Characterization of Metformin Proniosomal Gel for Treatment of Diabetes Mellitus. Int.J.Pharm. Sci.Rev., 2012;15(2):108-114.

62. Ryan F. Donnelly et al., Hydrogel-forming microneedles enhance transdermal delivery of metformin hydrochloride, Journal of Controlled Release, 2018;285:142-151.

63. Ravi Teja Allena et al., Preparation and Evaluation of Transdermal patches of Metformin Hydrochloride using Natural Polymer for Sustained Release. Int.J.of Pharm.&pharm.Sci. 2012;4(3):55-62.

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