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An Overview of Formulation and Evaluation of Meglinitide Class Transdermal Patches

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Abstract

Transdermal patches as a drug delivery system have received a lot of interest because of theircapacity to enable regulated drug release and improve patient compliance. This reviewarticleisbased on the formulation and evaluation of transdermal patches to deliver meglitinide-classantidiabetic drugs used to treat type 2 diabetes mellitus. Transdermal patches of meglitinide-classare a viable alternative to oral delivery, with the potential to reduce gastrointestinal adverseeffects and first-pass metabolism. This review begins with the introduction of diabetes mellitus, its types, the mechanism of action, the pharmacological profile of the Meglinitide class, anditsimportance in diabetes care. The Selection of appropriate polymers, permeation enhancers, andplasticizers, can affect drug release profile and skin permeability. The evaluation methodologiesfor transdermal patches were thoroughly evaluated, and it was concluded that meglitinideclasstransdermal patches were helpful in managing type 2 diabetes mellitus.

Keywords – Diabetes mellitus, Transdermal Patches, Meglinitide class

Introduction

Diabetes mellitus (DM) is the most prevalent endocrine illness, affecting over 100millionindividuals globally (6%). A disorder in which the body's capacity to produce or respondtothehormone insulin is reduced, resulting in improper carbohydrate metabolismand highbloodglucose levels. It has been shown to affect various physiological systems, includingbloodvessels, eyes, kidneys, the heart, and nerves [1]. Diabetes is divided into two types: insulin-dependent diabetes mellitus (Type I) and non-insulin-dependent diabetes mellitus (TypeII). Type 1 diabetes is also known as ketosis-prone or juvenile-onset diabetes. It is an autoimmunedisease that starts with a local inflammatory response in and around the islets, followedbytheselective death of insulin-secreting cells. It is often

characterized by the presence of anti-glutamic acid decarboxylase, islet cells, or insulin antibodies, which identify the autoimmunemechanisms that cause beta-cell death [2]. The pace of beta cell breakdown varies greatly; it might occur quickly in some persons and slowly in others [3]. The specific etiology of diabetesmellitus remains unknown [4]. Type II diabetes, often known as adult-onset diabetes, isdistinguished by peripheral insulin resistance and decreased insulin secretion [5]. Diabetesincreases the risk of a variety of consequences, including cardiovascular disease, peripheral vascular disease, stroke, neuropathy, renal failure, retinopathy, blindness, and amputations [6]. The increasing insulin secretion deficiency in the context of insulin resistance (AmericanDiabetes Association, 2014) [7]. Insulin resistance is common among people with this kindofdiabetes [8]. The reasons are multifaceted, and predisposing factors include obesity, a sedentarylifestyle, rising age (affecting middle-aged and older persons), and genetics. These patients areat a higher risk of having macrovascular and microvascular problems [9, 10]. Drugs are generallyused to save lives and treat symptoms. Secondary goals include preventing long-termdiabetesproblems and increasing longevity through the elimination of numerous risk factors. Insulinreplacement therapy is the primary treatment for people with type 1 diabetes, whereas foodandlifestyle changes are regarded as the cornerstones of type 2 diabetes treatment and management [11]. According to the International Diabetes Federation (IDF), India has around 40.9million diabetics, with a projected increase to 69.9 million by 2025 [12]. The pancreas secretes insulinand glucagon. The islets of Langerhans include beta (ß) and alpha (α) cells that release insulinand glucagon, respectively. Insulin reduces blood glucose levels by glycogenesis and deliversglucose to muscles, liver, and adipose tissue. Alpha (α) cells produce glucagon, which regulatesblood glucose levels by increasing glycogenolysis [13,14]. Insulin is not required byneural tissue or erythrocytes to use glucose. Meglitinides (Nateglinide, Repaglinide, Mitiglinide) areoral antihyperglycemic drugs, that promote insulin release in pancreatic beta cells by inhibitingATP-dependent potassium channels in their plasma membranes. The decreased potassiumeffluxdepolarises the cell membrane and activates voltage-gated calcium channels, resultinginincreased calcium ion input and insulin release [15]. Meglitinides class of drug promotes insulinrelease from beta cells in three distinct ways that sulfonylureas do not. First, it binds toadifferent receptor region on the beta-cell membrane than the sulfonylurea receptor site[16]. Second, it does not cause direct insulin exocytosis independent of ATP-sensitive potassiumchannels[16]. Third, unlike sulphonylureas, it can overcome the metabolic stress causedbydinitrophenol, making it more effective in normalizing glucose-induced insulin releaseinmetabolically stressed pancreatic islets [17]. It has a half-life of one hour. Furthermore, theMeglitinide class of drug has a limited oral bioavailability (56%), owing to the significant hepatic first-pass impact. It is administered at a dose of 0.5 to 4 mg three to four times a day. Themelting point is 130-131◦C, with a molecular weight of 452.58 [18]. Meglitinide class of topical drug use may assist the patient by minimizing side effects and preventing hepatic first-passmetabolism. To address these concerns, transdermal drug administration was determinedtobeappropriate. It offers many advantages such as the elimination of gastrointestinal discomforts andfirst-pass metabolism of the drug as compared to the conventional systems. So, this routeisconsidered one of the most preferable drug delivery routes for many of the drugs. Transdermal drug delivery system (TDDS) has generated significant interest indrugadministration through the skin for both local therapeutic effects on sick skin (topical delivery)and systemic drug delivery [19]. The skin provides several important benefits over manyotherroutes of drug administration, including the potential to avoid difficulties with gastrointestinal irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism, thereby increasingthe bioavailability of the drug, reduce the risk of systemic side effects by minimizingplasmaconcentrations compared to oral therapy, provide a sustained release of drug

at the siteofapplication; rapid Transdermal administration can also avoid pulsed entrance into the systemiccirculation, which can typically result in negative side effects [20].

BASIC COMPONENTS OF T. D. D. S

Nirav S et al., 2011 explained different components of the transdermal drug delivery system[21]

1. Polymer Matrix The polymer regulates how the drug is released from the device.

a) Natural polymers: cellulose derivatives, zein, gelatin, shellac, waxes, proteins, gums andderivatives, natural rubber, starch etc.

b) Synthetic Elastomers: Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrene Butadiene rubber, Neoprene, and others.

c) Synthetic polymers include polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethyl methacrylate, and epoxy.

2. Drug

To effectively construct a transdermal drug delivery system, the drug should be carefullyselected.

The following are some desired properties of drugs for transdermal delivery.

Physicochemical Properties

1. The drug's atomic weight ought to be less than 1000 daltons

2. The drug should have an affinity for both the lipophilic and hydrophilic phases. Extremepartitioning features are not favorable to effective drug administration via the skin.

3. The drug ought to have a low dissolving point. Along with these features, the drug shouldbestrong, have a short half-life, and be non-irritating.

4. Permeation Enhancers These are compounds that improve skin permeability by changing the skin's barrier, allowingadesired penetrant to pass through.

A)Solvents These chemicals improve penetration by eating the polar route and/or fluidizing lipids. Examples Water alcohols: methanol and ethanol; Alkyl methyl sulfoxides: dimethyl sulfoxide; alkyl homologs: methyl sulfoxide dimethyl acetamide

B) Other excipients

a) Surfactants These chemicals are thought to improve polar route transport, particularly of hydrophilic drugs. A surfactant's capacity to modify penetration is determined by its polar head groupandhydrocarbon chain length .

1 Anionic surfactants include dioctyl sulfosuccinate and sodium lauryl sulfate.

2 Nonionic surfactants include Pluronic F127 and F68, among others.

3 Bile salts include sodium ms taurocholate, sodium deoxycholate, and sodiumtauroglycocholate. b) Miscellaneous chemicals. These ingredients include urea, N-dimethyl-m-toluamide, calciumthioglycolate, and anticholinergics. Some potential permeability enhancers have recentlybeendescribed, however, published proof of their efficacy is sparse. Examples include eucalyptol, di-o-methyl-ß-cyclodextrin, and soybean casein .

C) Adhesives: Until now, all transdermal devices have been fastened to the skin with a pressure-sensitive adhesive that can be placed on the device's face or back and extends peripherally.

D) Backing membrane: Backing membranes are flexible and provide a good bond with thedrugreservoir, preventing the drug from exiting the dosage form via the top and allowing printing. Metallic plastic cover, plastic backing with permeable cushion, and occlusive base plate(aluminum thwart) are illustrations of impermeable materials that secure products whentheyare connected to the skin, as is cement

froth cushion (adaptable polyurethane) with occlusivebase plate.

Preparation of Meglinitide class Transdermal Patch

Meglinitide class of drugs such as repaglinide is prepared by solvent casting process andis usedto manufacture Repaglinide-inclusion complex-loaded matrix-type transdermal patches. Di-butyl phthalate was used as a plasticizer at a concentration of 20% w/w of the polymer dry weight. Thebacking membrane was formed by pouring and then evaporating a 4%aqueous solutionofpolyvinyl alcohol in a petri dish containing glycerin at 60°C for 6 hours. The drug matrixwascreated by dissolving various polymers (PVP with HPMC, EC, or Eudragit L100) invaryingratios with drug complexes in dimethylformamide solvent. The uniform dispersion was createdby slowly swirling with a magnetic stirrer. A homogenous solution including a plasticizer waspoured over the prepared backing membrane. The dispersion was progressively evaporatedat 40°C for 2 hours to produce a drug-polymer matrix patch. After complete drying, the patcheswere taken from the petri dish and stored in desiccators until usage [22].

Evaluation of Transdermal patches

1. Folding endurance
   A portion of the strip (2x2 cm) was repeatedly sliced and folded until it broke. The foldingendurance was evaluated by counting the number of times the film was folded in the samelocation, either to break it or to generate visible fissures [24, 25].
2. Tensile Strength
   The malleable quality of the fix was measured with a tensiometer. It contains two grasps forstack cells. The bottom one remains settled, but the higher one may be balanced. Filmstripsof2x2 cm were embedded between the cell grasps, and the constraint was slowly connecteduntil the film snapped. Pliable quality was evaluated utilizing a dial perusing in kilograms [23].
3. Percentage elongation break test
   The percentage elongation break was estimated by measuring the length shortly

beforethebreaking point and applying the following formula [26,27]. Percentage Elongation = Final length of strip − Initial length of strip x100 Initial length of the strip

4. Thickness
   The thickness of the transdermal patches was measured at three distinct locations with a digital micrometer screw gauge, and the mean value and standard deviation were computed [24, 28].
5. Drug content
   A 2x2 cm transdermal patch was dissolved in 100 cc methanol and shaken continuouslyfor 24hours. The whole solution was then ultrasonicated for 15 minutes. Following filtering, thedrugconcentration was determined using spectrophotometry at a wavelength of 292 nm[29]. Percentage Moisture Content = Initial weight − Final weight x100 Final weight
6. Percentage moisture uptake
   Individual transdermal films were weighed and placed in a desiccator with a saturated potassiumchloride solution to maintain 84% RH at room temperature for 24 hours. After 24 hours, thefilms were reweighed, and the % moisture absorption was determined using the technique [24]. Percentage Moisture Uptake = Final weight − Initial weight x100 Initial weight
7. Swelling study
   Individual transdermal patches (W1) were weighed and incubated at 37±0.5°C on a 2%agar gel plate. The patches were withdrawn from the petri dish at 15-minute intervals for up to1hour, and any excess water on the surface was carefully removed using filter paper. The swollenpatches were reweighed (W2), and the swelling index was calculated following the protocol [30,31].

   Swelling index = W2 − W1 x 100 W1

Conclusion

Meglinitide class of drugs such as Repaglinide, the first prandial glucose regulator approvedforuse in type 2 diabetes patients, has a better safety and effectiveness profile than existingoral antidiabetic drugs. It works quickly and has a short half-life. Transdermal administrationisanappealing alternate route for drugs that have limited bioavailability due to substantial first-passmetabolism. This review demonstrates that the transdermal patch of the meglitinide class of drugis developed to achieve improved therapeutic efficiency by regulating drug release, thereforeenhancing patient compliance and boosting bioavailability with less dose and fewer adverseeffects. The formulation and assessment of transdermal patches provide a promising optiontoimprove treatment outcomes in type 2 diabetes management. Future research should focusonoptimizing formulation components, improving skin permeability, and performing large-scaleclinical trials to determine the practicality of this delivery method in clinical practice.

References

1. Ismail, M.Y., Clinical evaluation of antidiabetic activity of Trigonella seeds andAeglemarmelos Leaves, Worl Appl Scien J., 7(10): 1231-1234 (2009)

2. WHO. Study Group Diabetes Mellitus, Technical report series no.727, WorldHealthOrganisation, Geneva, 1985.

3. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: associationwith birth weight, maternal obesity, and gestational diabetes mellitus Pediatrics, 2005, 115.

4. Wassmuth R, Lernmark A. The genetics of susceptibility to diabetes, ClinImmunol, Immunopathol. 1989; 53:358- 399,

5. Arora, S., Ojha, S.K., Vohora, D., Characterisation of Streptozotocin induced diabetesmellitus in Swiss Albino mice, Glo J of Pharmacol., 3(2): 81-84 (2009)

6. Jothivel, N., Ponnusamy, S.P., Appachi, M., Antidiabetic activities of methanol leafextract of Costus pictus D. Don in alloxan-induced diabetic rats, J of health sci.,53(6): 655-663 (2007).

7. Leonardo Jacob S, Pharmacology. The national medical series fromWilliams andWilkins Bartiarco, Hong Kong, London, 3rd edition, 1987, 221-225.

8. Blood A, Hayes TM, Gamble DR. Register of newly diagnosed diabetic children, BMJ. 1975; 3:580-583.

9. Tripathi KD. Essentials Medicals Pharmacology, Jaypee Brothers Medical Publisher (P)LTD, 7th edition, 2013, 258-281.

10. Dyck PJ, Kratz KM, Karnes JL. The prevalence by staged severity of various typesofdiabetic neuropathy retinopathy and nephropathy in a population-basedcohort: theRochester Diabetic Neuropathy Study, Neurology, 1993; 43:817-24.

11. Bastaki, S., Review Diabetes mellitus and its treatment, Int J Diabetes &Metabolism, 13: 111-134 (2005)

12. Bacchetta R, Passerini L, Gambineri E, Dai M, Allan SE. Defective regulatoryandeffector T cell functions in patients with FOXP3 mutations, J Clin Invest. 2006; 116:1713-1722,

13. Wassmuth R, Lernmark A. The genetics of susceptibility to diabetes, ClinImmunol, Immunopathol. 1989; 53:358- 399,

14. Atkinson MA, Eisenbarth GS. Type 1 diabetes new perspectives on disease pathogenesisand treatment, Lancet. 2001; 358:221-229.

15. Guardado-Mendoza R, Prioletta A, Jiménez-Ceja LM, Sosale A, Folli F. The roleofnateglinide and repaglinide, derivatives of meglitinide, in the treatment of type 2 diabetesmellitus. Arch Med Sci. 2013 Oct 31;9(5):936-43. doi: 10.5114/aoms.2013.34991. Epub2013 Apr 30. PMID: 24273582; PMCID: PMC3832818.

16. J Fuhlendorff, P Rorsman, H Kofod, C L Brand, B Rolin, P MacKay, RShymko, RDCarr; Stimulation of insulin release by repaglinide and glibenclamide involves bothcommon and distinct processes.. Diabetes 1 March 1998; 47 (3): 345–351.

17. Kofod H, Fuhlendorff J. Effect of repaglinide on insulin release in isolated isletsofLangerhans is unaffected by metabolic stress induced by dinitrophenol. Eur. J. Endocrinol. 1995;132:14.

18. Prajapati ST, Patel CG, Patel CN. Research Article Formulation and EvaluationofTransdermal Patch of Repaglinide.

19. Monika B, Amit R, Sanjib B, Alisha B, Mihir P, Dhanushram T. Transdermal drugdelivery system with formulation and evaluation aspects: overview. Res J PharmTechnol. 2012;5(9):1168–76.

20. Prithviraj C, K DB, Sanjib B, Suresh T, Sudip D. Design , Development , Physicochemical and In Vitro Evaluation of Transdermal Patches Containing Verapamil Hydrochloride in Ethyl Cellulose - Povidone Matrices. Res J PharmTechnol. 2009;2(1):168–72.

21. Nirav S. Sheth and Rajan B. Mistry. 2011. Formulation and evaluation of transdermal patches and to study permeation enhancement effect of Eugenol. 2011; 1(3): 96-101.

22. Mukherjee B, Mahapatra S, Gupta R, Patra B, Tiwari A, Arora P. A comparison betweenpovidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrixpatches based on in vitro skin permeation. Eur J Pharm Biopharm. 2005 Apr;59(3):475–83.

23. Shivaraj A, Selvam RP, Mani TT, Sivakumar T. Design and evaluation of transdermal drug delivery of ketotifen fumarate. Int J Pharm Biomed Res 2010;1:42–7.

24. Keleb E, Sharma RK, Mosa EB, Aljahwi A-AZ. Transdermal drug delivery system-design and evaluation. Int J Adv Pharm Sci 2010;1:201–11.

25. Bangale GS, Rathinaraj BS, Rajesh KS, Shinde GV, Umalkar DG, Rajveer CH, et al. Design and evaluation of transdermal films of atenolol. J Chem PharmRes 2010;2:593–604.

26. Lec ST, Yac SH, Kim SW, Berner B. One way membrane for transdermal drug deliverysystems/system optimization. Int J Pharm 1991;77:231-7.

27. Venkateswari Y, Jayachandra Babu R, Sampathkumar D, Mittal N, Pandit JK. Development of a low cost tetracycline strip for long term treatment of periodontal disease. Indian Drugs 1995;32:205–10.

28. Pandit V, Khanum A, Bhaskaran S, Banu V. Formulation and evaluation of transdermal films for the treatment of overactive bladder. Int J Pharm Tech Res 2009;1:799–804.

29. Garala KC, Shinde AJ, Shah PH. Formulation and in vitro characterization of monolithicmatrix transdermal systems using HPMC/Eudragit S 100 polymer blends. Int J PharmPharm Sci 2009;1:108–20.

30. Nishad KM, Arul B, Rajasekaran S. Design and comparative evaluation of clarithromycingastric bioadhesive tablets by ex vivo and in vivo methods. Asian J PharmClinRes2018;11:248–56. 31. Pandey S, Shah RR, Gupta A, Arul B. Design and evaluation of buccoadhesive controlledrelease formulations of prochlorperazine maleate. Int J Pharm PharmSci 2016;8:375–9.