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Review Article

Nanovesicles via Transdermal route: an untrodden tactic for delivery of sulphonylureas antidiabetic drugs

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ABSTRACT

Oral route of delivery is so far the most important route for delivering the drugs. Sulphonylureas are antidiabetic classes of drug mainly delivered via the oral route but oral absorbtion is highly influenced by food intake, other drugs, hepatic first pass metabolism, gastrointestinal motility, etc. Hence an alternative route is needed such as transdermal route which can help reduce the side effects of certain sulfonylurea class of antidiabetic drugs and also to achieve a continuous, controlled and targeted drug delivery. The major barrier accompanying transdermal delivery (stratum corneum) the outermost envelope of the skin, can be combat by promoting drug diffusion by usage of vesicles or colloidal particles like liposomes, niosomes, ethosomes and transfersomes. Among these, the most efficient are transfersomes as it can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. This high deformability gives better penetration of intact vesicles. These vesicles can act as surrogates for low as well as high molecular weight sulphonylureas antidiabetic drugs.

Key words: *Sulphonylureas, vesicles, ultradeformabilty, stratum corneum*

INTRODUCTION

Diabetes mellitus Type 2 is a severe metabolic disorder delineated by high blood sugar[1] insulin resistance, and relative lack of insulin. It makes up about 90% of cases of diabetes, while other 10% are due to diabetes mellitus Type 1 and gestational diabetes. Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity. As of 2015 there were approximately 415 million people diagnosed with the disease compared to around 30 million in 1985[2]. There are different classes of antidiabetic drugs namely sulphonylureas, biguanides, thiazolidinediones, non sulphonylureas, peptide analogues, etc. Their selection primarily depends on nature of diabetes, situation of person, age, and other factors.Among these, sulphonylureas were the first oral medicine available for treatment of type 2 diabetes. They are still one of the pioneer choice of treatment for Type 2 diabetes mellitus[3]. Sulfonylureas have gone through several steps of progression and are categorized as first, second, or third-generation drugs. The main difference between the generations is the binding affinity to the sulfonylurea receptor. Each progressive generation requires lower dose and binds more tightly to the receptor.

Generations of Sulphonylurea include:

- First generation: carbutamide, acetohexamide, chlorpropamide, and tolbutamide.
- Second generation: glipizide, gliclazide, glibenclamide, glyburide, glibornuride, gliquidone, glisoxepide, and glyclopyramide.
- Third generation: Glimepiride
- Fourth generation (light-dependent): JB253 and JB558

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CURRENT TRENDS OF SULPONYLUREAS IN MARKET

Antidiabetic molecule has become largest selling formulation in domestic pharma retail market. Nowadays 2nd and 3rd generation sulphonylureas are available in market as tablets. These oral formulations are associated with many disadvantages. The various formulations available in market along with their drawbacks are enlisted in Table No. 1.

Table 1: Prevailing trend and associated detrimental of sulponylureas antidiabetic drugs

DRUG	MARKETED DOSAGE FORM	ASSOCIATED IMPEDIMENTS
Glibenclamide	Tablets micronized tablets	Drowsiness, decrease in sugar level, upper respiratory tract infection, nausea, diarrhea, abdominal pain
Gliclazide	Tablets (Modified release, controlled release, sustained release) and Capsules	Gastrointestinal disturbances, jaundice, stomach inflammation, vomiting, diarrhea
Glipizide	Tablets (Extended release, sustained release,controlled release)	Heart burn, tinnitus, loss of appetite, jaundice, disulfiram like reaction
Glimepiride	Immediate release and sustained release tablets, Capsules	Irritability, temporary visual impairment, weakness, headache, low blood sugar, gastrointestinal disturbances

DETRIMENTALS AFFLIATED WITH MARKETED FORMULATION:

Sulponylureas have potential to cause low blood sugar level[4] (hypoglycemia) usually after initial hours of oral uptake and thus is not suitable for elderly people, or people living alone or with occupations where low blood sugar can be dangerous. This occurs because metabolites generated are able to lower the blood glucose level[4]. Glyburide possess higher risk of hypoglycemia than others due to its more number of active metabolite and higher affinity to sulphonylureas receptors[5]. Some sulfonylureas are metabolised by liver metabolic enzymes (cytochrome P450)[6] and inducers of this enzyme system (such as the antibiotic rifampicin) can therefore augment the clearance of Sulfonylureas. In addition, some sulfonylureas are bound to plasma proteins and use of drugs that also bind to plasma proteins can release the sulfonylureas from their binding places, leading to increased clearance.

Due to inconstant half-life, some drugs have to be taken two or three times a day (e.g. tolbutamide). The short-acting agents are administered about 30 minutes before the meal, to establish maximum efficacy when the food leads to increased blood glucose levels. Moreover, it has side effects such as feeling or being sick, constipation or diarrhoea, weight gain[4] etc. Certain drugs such as fluconazole (Diflucan) may hinder metabolism of sulfonylureas, leading to an increased level of sulfonylureas in the blood[7]. In addition, it shows cross reactivity with drugs like carbonic anhydrase inhibitors, loop diuretics and thiazide diuretics[5]. Thereupon, transdermal system is effective in preventing initial hypoglycemic episodes, "first-pass" metabolism of drugs and fluctuations in plasma levels of drugs. It utilizes drug candidates with short half-life and low therapeutic index, cause easy termination of drug in case of toxicity, reduces dosing frequency and adorns patient compliance.

ADVANCES IN TRANSDERMAL DELIVERY OF SULPHONYLUREA ANTIDIABETIC DRUG

To overcome the problems of oral delivery many transdermal formulations were shaped. However, the dominant circumception accompanying transdermal delivery is the stratum corneum which prevents effective penetration of most of the drugs. This barrier nature of skin causes problem for transdermal delivery of the drugs to achieve effective plasma concentration[8]. To subside this, various chemical penetration intensification methods were used such as citral in Glibenclamide patches[9]; methanol, oleic acid and n-octanal in Glipizide patches[10]; polyethylene glycol, oleic acid and isopropyl palmitate in Gliclazide patches[11]. Complexating agents like β cyclodextrin were also employed to increase the permeation rate of Gliclazide.

Controlled delivery can also be achieved by using release control membrane like controlled release transdermal patches of glibenclamide using ethyl vinyl acetate (EVA)[12]. Despite these advantages precaution has to be taken in vehicle selection to ensure adequate solubility of drug and to overcome barrier property of stratum corneum. These chemical penetration enhancers are generally combined with incompatability issues in formulations and causes local irritation. Therefore, biochemical penetration intensification methods are used which mainly involves the usage of vesicles or colloidal particles[13], particularly transfersomes.

PROFICIENCY OF NANOVESICLES AS A CARRIER VIA TRANSDERMAL PATHWAY

Broadest 'pores' in the stratum corneum, measures around 30 nm or less on an average in diameter, in comparison to the minimum phospholipid vesicles diameter of around 100 nm[14,15]. To drive a vesicle through a smaller pore, the vesicle has to get deformed. Various vesicles for drug delivery are ethosomes,

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liposomes, niosomes, transfersomes etc. Ethosomes are phospholipid based elastic nanovesicles containing high content of ethanol (20-45%) as a permeation enhancer. Liposomes are uniform multilamellar spheroid structures that comprises of lipid, often phospholipids, forming the bilayer, whereas, Niosomes are non-ionic surfactant bilayer vesicular structure ranging between 10 to 1000 nm in size. Liposomes and Niosomes, are relatively rigid in nature and very less efficient in enhancing the drug transport across the skin. Therefore, to overcome this problem ultradeformable lipidic supramolecular aggregrates "Transfersomes" has been recommended as it consists of phosopholipids and surfactant as an edge activator to destabilize the lipid bilayer thereby increasing vesicle elasticity and fluidity. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. It can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. This high deformability gives better penetration of intact vesicles[16].

CHANGING FORMULATIONS PARADIGM OF SULPHONYLUREAS

Numerous vesicles have been employed for conveying sulphonylureas due to their biocompatibility, biodegradabilities, high entrapment efficiency (in case of lipophilic drug near to 90%) and protection of encapsulated drug from metabolic degradation.

Glimperide ethosomes provided reduction in side effects alongwith controlled drug release and showed the entrapment efficiency of 97.12%[17]. Glimepride lioposomal films showed maximum entrapment capacity of 41.9% and depicted 16.6% drug release after 1 hr and 26.8% after 12 hrs[18].

Glibenclamide nanotransfersomes indicated higher penetration capacity and elasticity. At 0.5 hr, it exhibited Cumulative Drug Release (CDR) of (219.86 ± 6.38 µg/cm^2) as compared to control (108.86 ± 1.44 µg/cm^2) and revealed 10.44 times more flux than control[19]. This may be attributed to increase in thermodynamic activity, increased skin vehicle partitioning of drug, alteration in the barrier properties of the skin and elasticity of vesicle membrane. Similarly, Glibenclamide nanoemulsion gel showed 3.92 fold increase in relative bioavailability compared to oral drug suspension[20].

Gliclazide ethosomes presented maximum in-vitro release of 96.06 ± 0.16 % in dialysis membrane and ex-vivo release of 79.67 ± 0.35 % in case of mice skin[21]. This verified the potential of ethosomes of being a safe and very efficient drug carrier for transdermal delivery of drug (Table No. 2).

This suggests the potential of nanovesicles to combat the stratum barrier and enhance penetrability to obtain rapid therapeutic drug levels in plasma at lower dose. The various nanotechnologies used alongwith its advantages is summarized in Table No. 2.

Table 2: Sulphonylureas in Research and Development Pipeline

S. N.	Drug	Nanotechnique Implemented	Advantages
1.	GLICLAZIDE	Ethosomes as transdermal delivery carriers	Better stability, more hypoglycemic effect, non irritant, better reduction in blood glucose level
2.	GLIBENCLAMIDE	Nano transfersomes	Greater penetration, increase bioavailability
3.	GLIMEPIRIDE	Ethosomes, liposomal films	Longer duration of action, more patient compliance, improve skin penetrability

CONCLUSION AND FUTURE PROSPECTS

Introduction of nanovesicles generates a new breakthrough for the transdermal delivery of sulphonylureas class of antidiabetic drugs as they are biocompatible, biodegradable made from natural phospholipid. They act as depot releasing their content slowly, easy to scale up, and do not involve lengthy procedure and unnecessary use of pharmaceutically unacceptable additives. It can be used for both systemic as well as topical delivery of sulphonylurea. Hence, the attempt to deliver these drugs to systemic circulation through transdermal route using vesicular carrier system anticipate numerous advantages such as counting a higher bioavailability, negligible gastrointestinal side effect, less long term effects due to smaller amounts of drug administered, and most importantly increased patient compliance (with availability of patch system) which is foremost in treatment of such a life-time disorder.

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