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CURRENT ADVANCES IN NANOTECHNOLOGY FOR DELIVERY OF ANTI-DIABETIC DRUGS: A REVIEW

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ABSTRACT: Diabetes mellitus (DM) is being one of the major causes of morbidity and mortality, which seriously threatens the health of human beings. Worldwide around 366 million people are found to be affected by diabetes. DM is a chronic condition associated with abnormally high levels of sugar (glucose) in the blood. Absence or insufficient production of insulin, or an inability of the body to properly use insulin causes diabetes. DM can be classified as either type 1 or type 2. Type 1 diabetes conditions or insulin-dependent, which treated by insulin therapy. Type 2 diabetes or non-insulin-dependent, which treated by oral hypoglycemic drugs. Conventional insulin and other oral anti-diabetic agents delivery associated with many drawbacks, the need for frequent monitoring of blood glucose, multiple insulin injections, and adjustment of insulin dosages, self-injection, and difficulties in using the vial and syringe technique are among the barriers to patient compliance. Most oral anti-diabetic drugs exhibit low oral bioavailability and need frequent dosing owing to short half-lives, resulting in poor patient compliance. Therefore, to overcome such drawbacks associated with conventional dosage forms, several research works have been made in the area of nanotechnology; nanoparticle-based drug delivery systems have considerable potential for the treatment of DM. This paper illustrates the various nanoparticles - based drug delivery systems that have been investigated by different researchers to provide more effective delivery of anti-diabetic drugs.

INTRODUCTION: Worldwide more than 366 million has been estimated to be affected by DM, and this number is expected to rise to 552 million by 2030 [1]. World Health Organization projects that diabetes will be the 7th leading cause of death in 2030. As of 2012, an estimated about 1.5 million deaths were directly caused by diabetes [2].

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DM is a chronic endocrine disorder characterized by chronic hyperglycemia, with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both[3]. The diabetes mellitus associated with several effects include long term damage, the dysfunction that leads to failure of various organs [4]. Several pathophysiological processes are involved in the development of diabetes. These include processes which lead to defects in the beta cell functions of the pancreas with consequent insulin deficiency and others that result in resistance to insulin action.

The disturbance of carbohydrate, fat and protein metabolism are due to the deficient action of

insulin on target tissues resulting from insensitivity or lack insulin [5]. Diabetes has been categorized mainly as type 1 and type 2. Type 1 DM is an insulin dependent condition, characterized by a deficiency of insulin due to the destruction of insulin-producing β- cells of islets of Langerhans by the autoimmune system in the pancreas. While, type 2 DM is a non-insulin dependent condition, distinguished as disorders of both insulin resistance and impaired insulin secretion by β-cells in the pancreas [6]. Treatment of type 1 DM is usually through insulin replacement therapy [7], while type 2 DM is treated by oral hypoglycemic drugs in combination with dietary as well as lifestyle changes. Insulin is recommended for type 2 DM when treatment by oral hypoglycemic drugs has been failed [8].

Complications of diabetes affect most of the organs in the body ranging from the heart, kidneys, and eyes. These complications include acute and chronic complications that need to be treated additionally to the treatment of hyperglycemia. Long-term complications of diabetes include macrovascular atherosclerotic disease including cardiac, cerebral, and peripheral vascular disease and microvascular complications, namely retinopathy, nephropathy, and neuropathy [9].

2. The drawback in Conventional Delivery of Anti-Diabetic Drugs: Most of the oral hypoglycemic drugs are available either in the form of tablets and capsules. However, these conventional dosage forms offer various limitations such as short duration of action due to their short half-lives, frequent dosing, risk of hypoglycemia, low bioavailability, high protein binding, gastric irritation, diarrhea, insolubility in water and do not comply with the safety and efficacy of the patients [10]. Subcutaneous administrations of insulin associated with various limitations like multiple insulin injections, self-injection, difficulties in using the vial and syringe technique, local tissue necrosis, infection, nerve damage, high cost, potential dosing errors and fear of painful injections are among the barriers to compliance for patients. These limitations revealed the limited accessibility of conventional dosage forms at the desired site of action, higher systemic toxicity, narrow therapeutic window, complex dosing schedule for long-term treatment and led to poor patient compliance [11]. Several research studies are going on in the area of nanotechnology with the aid of nanosize particles to overcome such limitations in the delivery of anti-diabetic drugs. There are various types of nanotechnology-based drug delivery systems including polymer-drug conjugates, micellar formulations, liposomes, nano-sized drug particles and protein-bound drugs [12].

This manuscript throws more light on the need for nanoparticulate drug delivery systems, their advantages, limitations and recent advances in the application of such drug delivery systems in the delivery of anti-diabetic drugs.

3. Nanotechnology-Based Drug Delivery: Nanotechnology can be defined as the science and engineering involved in the design, production, characterization, and application of materials, structures, and devices whose dimension is at length scales below 100 nm [13]. The application of nanotechnology to medicine is called 'Nanomedicine' [14]. In drug delivery, nanotechnology aids in drugs that have suffered poor bioavailability problems or that result in adverse effect when delivered through conventional dosage forms [15]. Nanosystems are mainly used in the drug delivery system to prolong or sustain the drug release, increase the bioavailability of poorly absorbable drugs, increase the stability of drugs and to achieve special delivery of drug at specific sites into the body [16]. Nanoparticles are defined as structures that have a length scale between 1 and 100 nanometers.

At this size, nanoparticles begin to exhibit unique properties that affect physical, chemical, and biological behavior. Modification of the physicochemical properties of nanoparticles makes it easily to be taken up by cells so that they can be successfully used as delivery tools for currently available bioactive drugs [17].

Nanoparticles encapsulated with a drug within the polymeric matrix or absorbed or conjugated onto the surface. They can target specific sites in the body such as the reticular endothelial system (RES) due to its nano size and have also shown potential for targeted and controlled drug delivery, also, to improve the efficacy of a drug with a physicochemical problem such as poor solubility [18].

As drug carriers, nanoparticles have the advantages of high stability, high carrier capacity, specific drug targeting, feasibility of incorporation of both hydrophilic and hydrophobic substances, limiting fluctuation within the therapeutic range, reducing side effects, decreasing dosing frequency, improving patient compliance and feasibility of variable routes of administration, including oral administration and inhalation [19].

For drug delivery different type of nanoparticles have been used, they include mainly solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, nanoshells, quantum dots (QDs) superparamagnetic nanoparticles and dendrimers [20]. Nanoparticles, in particular, are potentially promising in the treatment and management of the diabetic's disease.

3.1. Nanoparticles-Based Insulin Delivery: Currently, insulin replacement therapy is recommended for type 1 diabetics and type 2 diabetes when oral hypoglycemic drugs have been failed [21]. Conventional insulin formulations are available to be given subcutaneously using a needle. It is reported that only 20% of insulin reaches the liver following subcutaneous insulin injection [22]. Administration of insulin by multiple injections associated with poor patient compliance. Therefore, there is a significant interest in developing new methods for the delivery of insulin and to prolong the duration of its effect using nanotechnology. Nano medicine-based insulin delivery involves polymeric micelles, liposomes, dendrimer, solid lipid nanoparticles, and nanoparticles of biodegradable polymers [23, 24]. The slow release of insulin offered by the nanoparticles will extend the action of insulin and hence replace the need for multiple injections that are believed to be uncomfortable for patients and thus increasing patient compliance.

Also, due to their small size and easy mobility, nanoparticles have high intracellular uptake. These novel dosage forms protect insulin from enzymatic degradation in the adverse gastrointestinal (GI) environment, while also enabling easy transport and improving the pharmacokinetics, bioavailability and therapeutic efficacy after administration [25]. Over the past decades, several designs of oral insulin nanoparticles of polysaccharide chitosan and alginate polymer have been proposed by scientists and industrialists with several leading to the application of intellectual property protection.

Chitosan, in particular, has been widely formulated into the nanoparticulate system for oral insulin delivery [26]. In the literature, several approaches for alternative routes of insulin administration have been developed, such as oral, buccal, nasal, rectal, pulmonary, ocular, transdermal, vaginal and intrauterine. However, the oral insulin administration seems to be the most convenient and physiologically advantageous [27]. Many authors have described the nanoparticle formulations for insulin delivery systems are discussed below.

Mukhopadhyay *et al*., developed self-assembled chitosan-insulin nanoparticles for successful oral insulin delivery. The encapsulation efficiency of insulin within the nanoparticles was found to be 85%. *In vitro* drug release study showed that the nanoparticles were also efficient in retaining a good amount of insulin in simulated gastric condition, while a significant amount of insulin release was noticed in simulated intestinal condition. The result revealed that the oral administrations of chitosan-insulin nanoparticles were effective in lowering the blood glucose level of alloxan-induced diabetic mice [28].

Zhao *et al*., prepared and optimized insulin-chitosan nanoparticles (ICNPs) using response surface methodology. The entrapment efficiency of the prepared nanoparticles was 93.1 %. The particle size of nanoparticles was between 91.3 ± 7.9 and 220.2 ± 9.5 nm and the average zeta potential was 14.4 ± 2.9 mv. More than 16.8% of the total drug was released rapidly in the first 1 h. After that, the insulin trapped in chitosan nanoparticles was released into the medium slowly and more than 93.0 % was released completely within 24 h [29].

Liu *et al*., formulated insulin-mixed micelles-loaded solid lipid nanoparticles (Ins-MM-SLNs) by a novel reverse micelle-double emulsion method, in which sodium cholate and soybean phosphatidylcholine were employed to improve the liposolubility of insulin, and the mixture of palmitic acid and stearic acid were employed to prepare insulin-loaded solid lipid nanoparticles (Ins-MM-

SLNs). The particle size and zeta potential were 114.7 ± 4.68 nm and -51.36 ± 2.04 mv, respectively [30].

Iwanaga *et al*., study the potency of surface coating liposomes with some materials for oral delivery of insulin. *In-vitro* release of insulin from liposomes in the bile salts solution was markedly reduced by coating the surface with the sugar chain portion of polyethylene glycol (PEG-Lip) or mucin (Mucin-Lip). Encapsulation of insulin into Mucin-Lip and PEG-Lip completely suppressed the degradation of insulin in the intestinal fluid. These results revealed that surface coating liposomes with PEG or mucin gained resistance against digestion by bile salts and increased the stability in the gastrointestinal tract [31].

Cue *et al*., prepared PLGA nanoparticles (PNP) and PLGA-Hp55 nanoparticles (PHNP) as carriers for oral insulin delivery by a modified emulsion solvent diffusion method. The particle sizes of the PNP and PHNP were 150 ± 17 and 169 ± 16 nm, respectively, and the drug recoveries of the nanoparticles were 50.30 ± 3.1 and 65.41 ± 2.3%, respectively. The initial release of insulin from the nanoparticles in simulated gastric fluid over 1 h was 50.46 ± 6.31 and 19.77 ± 3.15%, respectively. The relative bioavailability of PNP and PHNP compared with subcutaneous (S.C.) injection (1 IU/kg) in diabetic rats was 3.68 ± 0.29 and 6.27 ± 0.42%, respectively. The results show that the use of insulin-loaded PHNP is an effective method of reducing serum glucose levels [32].

3.2. Nanoparticles - Based Delivery for Hypoglycemic Drugs: Most of the oral hypoglycemic drugs are available either in the form of tablets and capsules. However, these dosage forms offer various untoward adverse effects and limitations. These adverse effects revealed the limited accessibility of conventional dosage forms at the desired site of action, higher systemic toxicity, narrow therapeutic window and complex dosing schedule for long-term treatment [33]. Limitations associated with oral hypoglycemic offered the opportunities for the investigators to develop new delivery systems having improved therapeutic efficacy. Novel drug delivery carrier systems are developed to deliver anti-diabetic drugs safely and more precisely to the specific site for the scheduled period of time in a controlled manner for better therapeutic effectiveness and better control over diabetes mellitus.

Additionally, alteration in physicochemical and pharmaceutical properties of anti-diabetic drugs has avoided/modified the biological barriers that limit the availability of actives to the various therapeutic targets. While many of investigations have been carried out, strategies to come up with the appropriate carrier systems for anti-diabetic delivery are still being made to get widespread recognition in the global market [34]. In the recent decades, nanoparticles have attracted many attentions as nanotechnology-based drug delivery systems. Their potential advantages such the possibility of controlled drug release, targeting, proper incorporation of lipophilic as well as hydrophilic drugs, remarkable biocompatibility, low biotoxicity and capability of avoiding organic solvents in the production cycle and ease of scale-up, have provoked many research projects exploiting the possible use of these nanostructures in drug delivery [35]. A review of nanoparticles formulations for oral hypoglycemic drugs investigated by different investigators has been described in this section.

Sharma *et al*., develop metformin solid lipid nanoparticles (M-SLNs) and incorporate it in the transdermal patches. M-SLN was prepared by solvent diffusion technique. Zeta potential of the best formulation was found to be +27mv. Drug content was found to be 1.45 mg/patch. The *ex-vivo* permeation studies indicate that the high cumulative amount of drug is permeated from M-SLNs. These results provided evidence for developing transdermal metformin for human applications [36].

Behera *et al*., prepared rosiglitazone-loaded PLGA nanoparticles by emulsification solvent evaporation technique by using a biodegradable polymer, poly (D, L-lactic-co-glycolic acid) (PLGA) as a sustained release carrier. The drug release pattern consisted of two phases releasing about 40% (within first 24 hr) followed by a slow releasing phase (up to 90%) within the next 48 h [37].

Borkhataria and Patel develop and evaluate pioglitazone HCl-loaded chitosan nanoparticles by ionic gelation of chitosan with tripolyphosphate

anions at various concentrations. The particle size of all the prepared formulations was in nano-range (250 - 503 nm) with zeta potential (+30.70 to +40.50 mv). The encapsulation efficiency and the drug loading capacity were 54-77% and 29-52%, respectively. The *in-vitro* release profile of pioglitazone HCl from the nanoparticles showed a sustained release of the drug throughout 20 h. The results revealed that pioglitazone HCl-loaded chitosan nanoparticles appear to be effective in the management of the anti-diabetic activity [38].

Lakshmi *et al.*, prepared and characterized repaglinide loaded ethyl cellulose nanoparticles by the solvent evaporation method. The prepared NPs showed 86.4% encapsulation efficiency and 9.61% drug loading. The *in-vitro* release profile of drug from the NPs was characterized by a delayed release phase. The results suggest that nano-encapsulation of the drug in the biodegradable, biocompatible polymer will improve its pharmacological significance [39].

Ebrahimi *et al*. prepared repaglinide-loaded solid lipid nanoparticles (SLNs) using the solvent diffusion method. The results showed that the mean zeta potential was -17 ± 3 mv and the mean particle size of SLNs was 210 ± 16 nm. *In-vitro* release data revealed at least 24 h release time with mild burst release [40].

Naik developed sustained release nateglinide-loaded ethyl cellulose nanoparticles and characterized the properties of recovered nanoparticles. The sustained release nanoparticles were prepared by oil in water single emulsion solvent evaporation method. The highest particle size and encapsulation efficiency of recovered nanoparticles were 248.37 nm and 91.16% respectively. The recovered nanoparticles are spherical in nature and uniform in size. Developed nanoparticles have low crystallinity than pure nateglinide. The highest drug-polymer ratio formulation showed drug release 61.1 ± 1.76% up to 24 hr [41].

Alkem *et al*., formulated gliclazide - loaded chitosan nanoparticles (NPs) by salting out of chitosan with sodium citrate. The prepared NPs showed high drug loading capacity and encapsulation efficiency. It was revealed that the developed NPs prolonged the drug release throughout 24 h with an initial burst effect followed by sustained release. The rate and amount of the drug release were decreased as the polymer content increased [42].

Devarajan and Sonavane formulated gliclazide-loaded Eudragit nanoparticles (Eudragit L100 and Eudragit RS) as a sustained release carrier with enhanced efficacy. The developed Eudragit nanoparticles (L100 and RS) showed high drug loading and encapsulation efficiencies. Dissolution study revealed the sustained release of gliclazide from Eudragit L100 as well as Eudragit RS NP. Developed Eudragit NPs revealed a decreased t_{min} (ELNP), and enhanced bioavailability and sustained activity (ELNP and ERSNP) and hence superior activity as compared to plain gliclazide in a streptozotocin-induced diabetic rat model. The developed Eudragit (L100 and RS) NP could reduce dose frequency, decrease side effects, and improve patient compliance [43].

Dora *et al*., prepared glibenclamide-loaded Eudragit L100 nanoparticles (ELNPs) by the solvent displacement method. It was found that as drug concentration increases concerning polymer the drug loading capacity and encapsulation efficiency were found to be increased. Dissolution study revealed an increased release of glibenclamide from NPs. They also demonstrate a very significant change in the solubility in comparison with the pure drug. It was found that the developed ELNPs revealed a decreased t_{min} and enhanced bioavailability and hence superior activity as compared to simple glibenclamide in the alloxan-induced diabetic rabbit model. The prepared NPs could reduce dose frequency, decrease side effects, and improve patient compliance [44].

Mokale *et al*., prepared glimepiride-loaded nanoparticles using poly-D, L-lactide (PLA) as the polymer by o/w solvent evaporation method. Encapsulation efficiency and drug content were found to be 80.55%, and 40.27, respectively and the particle size of the nanoparticles was 442 nm. *In-vitro* drug release of the most optimized batch showed 73.72% to 78.12% drug released up to 12 h [45].

CONCLUSION: By using nanotechnology the nanoparticle-based drug delivery systems are being investigated for many years to overcome the limitations of conventional dosage forms of drugs. As a conclusion of this review paper, these advanced nanoparticles drug delivery systems are potentially beneficial for delivery of anti-diabetic drugs. Shortly, this nanoparticles based insulin delivery could replace the traditional subcutaneous insulin injections. Nanoparticles delivery systems are designed to obtain controlled or prolonged drug delivery and to improve bioavailability as well as stability. Also, nanoparticles can also show several advantages like limiting fluctuations of drugs within the therapeutic range, reducing side effects related to conventional dosage form, protecting drugs from degradation, decreasing dosing frequency, improving patient compliance, convenience and help the better quality of living of DM patients.

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