



Latest Development of Administration Routes for Anti-Diabetic Agents using Insulin Nanoparticles (NPs)

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Abstract

For the latest development for anti-diabetic agents, nanoparticles (NPs) have been in focus. Permeation enhancers (PEs) are known to increase the oral absorption of various kinds of macromolecules. One of PEs would be sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC), which has been used for glucagon-like peptide-1 receptor agonist (GLP-1RA) as oral semaglutide (Rybelsus). For insulin encapsulation, polyelectrolyte nanocomplex (PEC) have been the promising carriers. Furthermore, spray drying technique has been an adequate and well-known industrial method for developing pharmaceutical industries, and aqueous polymer dispersions (APDs) have been applied. Consequently, self-nanoemulsifying drug delivery systems (SNEDDS) can be expected to improve future diabetic treatment.

Keywords

Nanoparticles, Permeation Enhancers, Sodium N-[8-(2-Hydroxybenzoyl) Amino] Caprylate, Spray Drying, Aqueous Polymer Dispersions, Self-Nanoemulsifying Drug Delivery System

Abbreviations

NPs: Nanoparticles; PEs: Permeation Enhancers; SNAC: Sodium N-[8-(2-Hydroxybenzoyl) Amino] Caprylate; APDs: Aqueous Polymer Dispersions; SNEDDS: Self-Nanoemulsifying Drug Delivery System

Diabetes has been one of the most crucial common diseases which should be managed properly [1]. Recent pharmacological topics for diabetes include glucagon-like peptide-1 receptor agonist (GLP-1RA) [2]. Among several types of GLP-1 RAs, oral semaglutide has been in focus and introduced to medical practice with beneficial effects [3]. This novel agent was developed by 30 years of continuous research [4]. Oral administration became possible due to the co-

formulation of the peptide associated with the sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) which is an absorption enhancer [5]. For semaglutide, meaningful projects were found in three categories. They are i) Semaglutide Treatment Effect in People with Obesity (STEP), ii) Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN), and iii) Peptide InnOvation for Early diabetes treatment (PIONEER) [6].

Permeation enhancers (PEs) have been known to increase the oral absorption of various kinds of macromolecules. One of PEs would be SNAC, which has been adapted to oral semaglutide (Rybelsus). However, some problems are present, where the bioavailability of the formulation is quite lower associated with variable involvement of enzymes, pH and other gastrointestinal (GI) barriers. From recent experiment, SNAC showed the ability of interacting with insulin for tight complex in the condition, in which i) insulin concentration $\geq 40 \mu\text{g/mL}$, ii) SNAC/insulin ratio $\geq 20:1$, iii) pH ≥ 6.8 from dependent manner [7]. Collectively, these results showed the insight for the interaction of PEs/payloads and for SNAC-based oral insulin drug delivery system (DDS) associated with higher oral bioavailability and beneficial medication guidance.

From various applications of dosage forms, insulin nanoparticles (NPs) associated with higher loading content were observed [8]. The purpose of the work was the evaluation of the impact of the spray drying process and freeze-drying for the insulin-loaded chitosan NPs. As a result, spray drying could bring about the dehydration of insulin NPs with no need for cryoprotectants. These processes have created an advantage for greater loading capacity associated with simple requirements and lower necessary costs in comparison with conventional approaches of freeze drying. When trying to deliver insulin particles via the oral route, the technology of nanoparticles (NPs) can offer significant advances [9]. As regards NP, some aggregation may decrease the bioavailability of insulin-loaded NP [10]. Recently, freeze-drying technology has been the standard method for creating stable NPs associated with preventing unpreferable changes in storage [11].

For insulin encapsulation, polyelectrolyte nanocomplex (PEC) is one of the promising carriers [12]. However, the dominating obstacles for smooth insulin delivery include enzymatic degradation of insulin and insufficient degree of penetration for mucosa and enterocytes. In these circumstances, PEC embedded microparticles have been fabricated to solve the dilemma mentioned above. PEC coated with sodium dodecyl sulfate (SDS) has been prepared and

then spray-dried by the matrix of various ratios of chitosan (CS)/ polyvinyl alcohol (PVA) for making the microparticles. Consequently, microparticles by CS/PVA would become a platform of enhanced oral administration of insulin delivery.

Nano-technology can be used for common agents for diabetes and dyslipidemia. Glimepiride (GLM) as oral sulphonylurea (SU), and simvastatin (SIM) for dyslipidemia have been prescribed so far. However, these agents may show problems with the dissolution rate of limited oral bioavailability. Then, it would be required to develop two different types of nanosuspension viz. nanoformulations, and also self-nanoemulsifying drug delivery systems (SNEDDS). In the latest report, these two agents of GLM and SIM have been co-formulated for nanosuspension (NS) in addition to SNEDDS [13]. These formulations have been spray dried for solidification and then estimated for the efficacy on glucose variability. As to the administration route of insulin, recent research has been found. Usually, insulin has been provided by injection so far. Alternative delivery routes include the needle-free method, associated with enhanced bioavailability and absorption. Related information was collected from employing several PubMed articles as well as supplementary manuscripts during 1958-2022. Various approaches for stable, easy and safe routes can be found, which are oral, intranasal, buccal, oral inhalation, ocular, transdermal, rectal or vaginal routes [14]. Thus, lots of approaches have been observed for the attempts to overcome pharmacological barriers of insulin delivery.

As to the subcutaneous route of insulin administration, it has always been invasive and caused discomfort and possible infection of the diabetic patients. Most suitable administration of insulin would be an alternative oral route. But it would be difficult due to a major barrier of this route, which is the rapid breakdown of insulin molecules by gastrointestinal enzymes [15]. Then, nanocarriers would be preferred in the light of oral insulin DDS. Among several types of nanocarriers, bio-polymeric nanocarriers have shown special impressive attention due to their non-toxic, hydrophilic and biodegradable characteristics. In recent years, increasing research for the alternative

insulin DDS has been observed. From various developments, research accomplishments of oral insulin DDS have reached the phase 3 level of clinical trials [16]. For decades, several types of transdermal insulin have been in focus. However, future novel insulin delivery DDS would show technological advancement.

Spray drying technique has been an inexpensive and well-known industrial method for making dry powder from liquid situations for the pharmaceutical industries [17]. In the process of spray drying, evaporation of water has been speedy, in which low temperature of the particle core can be kept [18]. From the pharmaceutical coating of multiparticulates and tablets points of view, Aqueous Polymer Dispersions (APDs) have been in focus [19]. APDs can avoid the hassles of organic solvents and offer the advantages of short processing times and lower viscosity. Then, they are involved in the process of fluidized-bed machinery. Another useful processing approach would be co-spray drying APDs with agents in aqueous method systems. It can bring matrix- and capsule-type microspheres with improved processing situation and controllable size in a single step. Consequently, each microsphere can be formulated into a different dosage type of form.

In summary, latest development of novel administration routes of anti-diabetic agents was introduced. Nano-technology may provide insulin via GI tract, which can be expected in common way near future.

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Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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Mini Review

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