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Review Article

Current trend in drug delivery considerations for subcutaneous insulin depots to treat diabetes

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder due to irregularities in glucose metabolism, as a result of insulin disregulation. Chronic DM (Type 1) is treated by daily insulin injections by subcutaneous route. Daily injections cause serious patient non-compliance and medication non-adherence. Insulin Depots (ID) are parenteral formulations designed to release the insulin over a specified period of time, to control the plasma blood glucose level for intended duration. Physiologically, pancreas produces and secretes insulin in basal and pulsatile mode into the blood. Delivery systems mimicking basal release profiles are known as open-loop systems and current marketed products are open-loop systems. Future trend in open-loop systems is to reduce the number of injections per week by enhancing duration of action, by modifying the depot properties. The next generation technologies are closed-loop systems that mimic the pulsatile mode of delivery by pancreas. In closed-loop systems insulin will be released in response to plasma glucose. This review focuses on future trend in open-loop systems; by understanding (a) the secretion of insulin from pancreas, (b) the insulin regulation normal and in DM, (c) insulin depots and (d) the recent progress in open-loop depot technology particularly with respect to nanosystems.

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1. Introduction

Insulin is an anabolic hormone regulating glucose metabolism, and its dysregulation leads to Diabetes mellitus (DM). The DM is a world health problem, and as per WHO fact sheet, 422 m people are affected in 2014, and among adults; it has increased from 4.7% in 1980 to 8.5% in 2014. Its prevalence is higher on low and middle income countries [1]. Clinically, DM is identified by elevated blood glucose level (BGL) and reduced plasma insulin. DM is of two types, Type-1 and Type-2. The Type-1 (T1DM) [2,3] is insulin dependent (IDDM), While, Type-2 (T2DM) is non-insulin dependent (NIDDM) [4,3]. If left unattended, long-term elevated BGL causes glycation of proteins and other cellular components. This affects various organs

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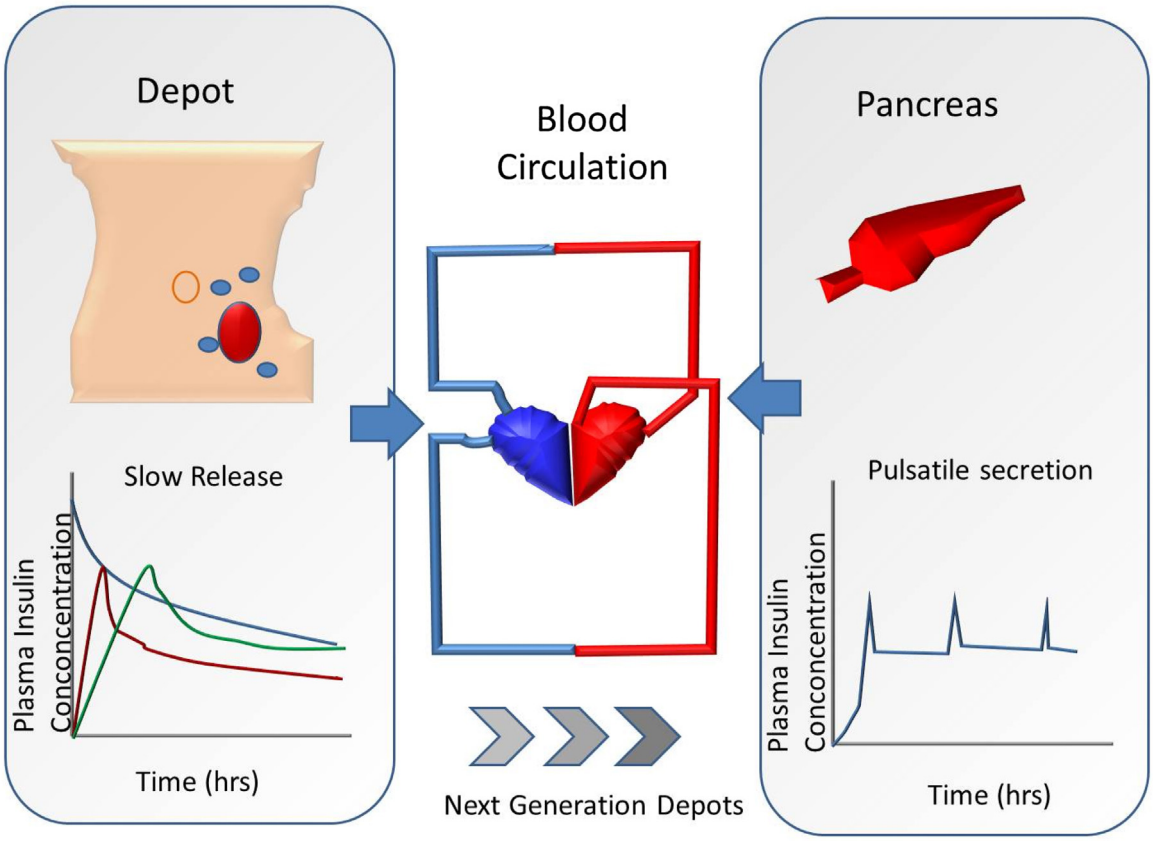

Fig. 1. Comparison between the insulin delivery by pancreas and subcutaneous insulin depot in abdomen to address insulin insufficiency in T1DM. Panel-1 shows the slow release of insulin from the injection site and reaching to blood circulation; the corresponding graph shows plasma insulin concentration, red line- short acting, green line- medium acting and blue line- long acting insulin. The panel-2 shows systemic circulation. The panel-3 shows the insulin secretion by the pancreas, the corresponding graph shows pulsatile plasma insulin profile. Broken arrow shows trend in next generation depots to mimic physiological delivery of insulin. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

causing retinopathy and nephropathy as well as numerous cardiovascular and neuropathic complications. Long-term anti-diabetic therapy is the suggested pharmacotherapy for keeping the BGL under control.

In T1DM, insulin insufficiency is addressed by giving exogenous insulin injections (Fig. 1). These injections are preferably given by subcutaneous (s.c.) route. Clinically, the other routes of administration are intramuscular (i.m.) and intravascular (i.v.). The daily injections are taken by the patient without medical supervision, for that s.c. route is most preferred to reduce vascular and neuronal damage. The injections conventionally are given as repeated injections on a daily basis to control BGL to normal limits. Its painful, causing serious patient non-compliance. The non-compliance leads to non-adherence to treatment, affects the effectiveness of insulin therapy. The Fig. 1 shows the overall picture of insulin injections that includes conventional repeated injections as well as new trends in injections. Future designs of insulin injections are looking for mimicking delivery of insulin by pancreas. To address these, new controlled delivery systems need to be developed. The purpose of this review is to analyze in detail the current trends in considerations for insulin delivery using subcutaneous depot. For that, the following factors are analyzed; (a) pancreatic insulin secretion, (b) insulin disposition (absorption, distribution, metabolism and elimination (ADME)) in normal and in DM, (c) exogenous insulin therapy using insulin depots, (d) insulin chemical and physical properties relevant for controlling the disposition, (e) insulin depots past, present and future.

2. Physiological insulin regulation

2.1. Pancreas and insulin secretion

The pancreas is a long flattened exocrine gland about 6 inches long located deep in the abdomen. This cone shaped organ is having a head region and tail region. The broader head of the pancreas is on the right side of the abdomen, connected to the duodenum through pancreatic duct and the narrow end of tail region extends to the left side of the body. This vital part of digestive system is responsible for production and exocrine secretion of insulin that controls the BGL [5]. The physiological secretion of insulin by pancreas is shown in Fig. 2. Pancreatic beta cells of Langerhans produce insulin [6]. In normal persons, the pancreas sense the glucose present in the plasma, and required amount of insulin is delivered to control BGL to normal levels [7,8]. Beta cells are clustered in pancreas and are surrounded by more number of blood vessels than normal leading to 10 times higher blood supply for easy nutritional exchange and detection of glucose [7,9]. Insulin secretion from beta cells initiates by fusion of intracellular insulin containing granules with the plasma membrane for laying off the granular content to the blood stream. Insulin secretion occurs in a characteristic biphasic pattern with a transient first phase followed by a sustained second phase release profile. Oral administration of glucose (75 g) raises plasma insulin from basal value (20–30 pmol/ L) to 250–300 pmol/ L in 30 min [7,10]. In humans, when plasma glucose reaches approx. 7 mmol, first phase insulin secretion reaches to the peak value of 1.4nmol/min, it lasts for 10 min followed by second phase with a