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Review

Improving the outcomes of biopharmaceutical delivery via the subcutaneous route by understanding the chemical, physical and physiological properties of the subcutaneous injection site

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ABSTRACT

Subcutaneous (SC) injection is currently the most common route of self-administering biopharmaceuticals such as proteins and peptides. While pharmaceutical scientists have acquired great skill in identifying formulations for these proteins and peptides with multi-year shelf life stability, the SC injection of these formulations can result in inconsistent or particularly low bioavailability outcomes. We hypothesise that upon injection, the chemical, physical and physiological properties of the subcutaneous tissue may play a crucial role in determining the therapeutic outcomes of SC injected biopharmaceuticals. We contend that physical and chemical stresses placed upon the injected protein or peptide as it transitions from the non-physiological environment of its formulation to the homeostatic conditions of the SC tissue can affect its fate following injection, and that by taking this environment into account when formulating, more precisely controlled release of SC injected biopharmaceuticals could be achieved. In this mini-review we describe how events that occur to an injected protein or peptide during this post-injection transition period could affect the diffusion of bioactive material to blood capillaries and lymphatic vessels. With this in mind, we have reviewed the chemical, physical and physiological attributes of the SC tissue and collated studies on how these properties are known to affect protein stability and diffusional properties. Finally, examples where the understanding of the properties of the SC tissue when formulating for SC injected biopharmaceuticals has improved the predictability of drug delivery via the SC route are discussed, with the need for novel tools for rational and informed formulation development highlighted.

Contents

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1. Introduction — subcutaneous tissue and variability of delivered biopharmaceuticals

The subcutaneous (SC) injection site is positioned below the dermis where it functions in energy storage and hydration as well as a thermal insulator and shock absorber to protect underlying musculoskeletal structures [1]. SC tissue is composed of two different tissue types: loose connective tissue, also known as areolar tissue, and underneath that, adipose tissue [2]. Blood capillaries to sustain the viability and nerve fibres with various types of endings to provide the skin with its critical sensory function permeate the SC tissue [3]. A lymphatic capillary bed resides within the SC space and there is very little proteolytic activity in the subcutaneous tissue [3]. These features make SC tissue an ideal route for administering biopharmaceuticals that are not suitable for oral delivery due to proteolytic degradation within and/or limited absorption across the epithelial barrier of the gastrointestinal tract. The SC route, however, introduces other uncertainties in drug delivery, such as variable bioavailability between different formulations and various injection sites of the body [4].

Patients are not administered drugs, they are administered formulations that contain a drug and subcutaneously injected biopharmaceuticals are often formulated in non-physiological conditions that function to improve shelf-life stability [5,6]. Indeed, biopharmaceuticals intended for SC injection are commonly formulated at acidic pH with a variety of stabilising agents [6,7]. One can assume that upon administration the SC injection site returns to homeostatic condition of the body, with the temporal parameters of this recovery being dependent upon injection volume and formulation composition. We hypothesise that this period of transition from the formulation environment to the homeostatic environment of the SC tissue can be detrimental for some biopharmaceuticals, in particular proteins and some peptides. Such detrimental changes to proteins and peptides injected into the SC space, due to alterations in their structural properties, could adversely affect their functional properties. Further, we hypothesise that these changes could alter the ability for an injected biopharmaceutical to be absorbed efficiently from the SC injection site. In summary, we propose that the impact of events during the time an injected biopharmaceutical transitions from its formulation conditions to the environment of the SC tissue can pose a stressful period that could affect stability, solubility, and function prior to its absorption into blood capillaries and/or lymphatic vessels. Further, we propose that with an improved understanding of the physical, chemical and biological properties of the subcutaneous injection, the fate of a SC injected biopharmaceutical can be controlled to a greater extent.

Our hypotheses related to the potential for a period of possible instability during the transition from the environmental conditions of an injected formulation to the homeostatic condition of the body provides a potential explanation for the observation that some proteins and peptides injected into the SC space have bioavailability outcomes that are unacceptably low or variable. In that light, the current review article aims to summarise the chemical, physical and physiological characteristics of the subcutaneous tissue, highlighting the need for considering not only shelf-life stability but also the properties of the subcutaneous tissue in the optimization of protein and peptide formulations intended for SC injection. A second aspect of the review aims to illustrate how characteristics of the SC injection site may affect pharmacokinetic and/or pharmacodynamic profiles of biopharmaceuticals following SC injection. Finally, the future perspectives of SC drug delivery, current formulation strategies where the combination of formulation approaches and the SC injection site properties are utilised for controlled delivery of biopharmaceuticals, and emerging analytical techniques for enhancing the efficacy of SC drug delivery are highlighted in the last part of the review article. It is important to note that this mini-review focuses on events occurring shortly after the injection; longer term adverse effects, such as immunogenicity that may or may not be a result of the potential post-injection stability issues [8] are outside the remit of the current review.

2. Physiological, physical and chemical properties of the subcutaneous injection site

The major physiological and chemical features of the subcutaneous tissue are schematically presented in Fig. 1, and summarised in Table 1. These are the extracellular matrix formed by collagen, hyaluronic acid and chondroitin sulphate, the interstitial fluid, the temperature of the tissue and hydrostatic and osmotic pressure. From this diagram, it can be appreciated that the SC injection site contains an organisation of collagen proteins that provides a lattice network to support integrated elements of polysaccharides. These are discussed in detail in the following section.

2.1. Extracellular matrix

When the extracellular matrix (ECM) was first discovered, it was described as “an amorphous ground substance” [9]. However, as the understanding of the functional properties of the ECM organisation improved it became obvious that it is a highly ordered structure with collagen providing mechanical stability in the form of a three dimensional network, and glycosaminoglycans, most commonly hyaluronic acid and chondroitin sulphate, filling the void spaces within the collagen network [10]. Specific elements of the ECM and their main properties are briefly summarised in Table 2, and will be discussed in detail in the following sections of the paper.

2.1.1. Collagen

Collagen is the most abundant protein within the body of mammals and forms fibrous structures that function as structural elements in the ECM, tendons and basement membranes [11]. There are several types of collagen undertaking different functions in the body that can be grouped according to the function they have in the body: fibril forming collagens (I, II, III, V and XI), fibril associated collagens (IX, XII and XIV), microfibrillar collagen (VI), short chain collagens (X and VIII) and basement membrane collagen (IV) [12]. The most prevalent collagens in loose connective tissue, such as that present in the SC injection site, are types I and III [13].

A generalised collagen structure is illustrated in Fig. 2. The common primary amino acid sequence for all collagen types is a repeating (glycine-X-Y) motif, where X and Y can be any amino acid but are frequently proline (Pro) or hydroxyproline (Hyp) residues [14]. The collagen polypeptide forms a left-handed helix with the glycine (Gly) residues positioned on the same axis throughout the helix. The iminoacid residues of Pro and Hyp sterically stabilise the secondary structure known as α-chain, and three α-chains form a triple helical, closely packed, supercoiled collagen fibril structure with the Gly residues packed inside the triple helix [15], as illustrated in Fig. 2. The Hyp residues also participate in stabilising the collagen fibril structure in aqueous solution by enabling water bridge formation between its hydroxyl groups located in adjacent α-chains [14,16]. The diameter of a typical