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Controlled-Release Preparation Containing Meglitinide for Treatment of Type-II Diabetes Mellitus

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Abstract

Meglitinides promote pancreas insulin secretion, and have a short half-life in plasma; they are often termed "short-acting-type insulin secretagogues". They primarily control postprandial blood glucose. On the basis of these characteristics, various controlled-release preparations containing meglitinides are currently being developed to achieve precise and/or timely control of blood glucose, or to reduce the dosing frequency, or to enable a more convenient administration route. If approved, it is hoped that they will increase quality of life for diabetes patients.

Keywords: Meglitinides; Blood glucose level; Controlled-release preparation

Introduction

Meglitinides are antidiabetic agents that primarily control postprandial blood glucose (PBG). As they have a short half-life in plasma, and promote short-term pancreatic insulin secretion [1-3], they are often termed "short-acting type insulin secretagogues". They include nateglinide [4,5], Repaglinide [6] and mitiglinide [7]. At present, commercially available meglitinide formulations are immediate-release preparations [4,5]. These are taken three times a day, immediately before meals. However, on the basis of the above pharmacokinetic and pharmacodynamic characteristics, meglitinides are considered to be suitable for use as active ingredients in controlled-release preparations for controlling blood glucose. There are demands for the following with respect to type-II diabetes medications: (1) sufficient and timely control of both PBG and fasting blood glucose (FBG); (2) control of early-morning high blood glucose; (3) reduction of dosing frequency; and (4) different administration route. The last two are in order to increase convenience. Since the first controlled-release nateglinide preparation was reported to control both PBG and FBG, in 2000 [8], There have been numerous reportsab out controlled-release meglitinide preparations. However, many pharmacological challenges remain for improved medications for type-II diabetes mellitus. In this review, aspects of formulation design and pharmacological efficacy are discussed with respect to controlled-release meglitinide preparations that are currently being developed.

Control of Both PBG And FBG, or Early-Morning High Blood Glucose

The first reports about an oral, controlled-release preparation containing nateglinide (12) for reduction of both PBG and FBG were reported by Makino et al. [1-3, 8-10]. They investigated enteric-coated granules [1,8-10] and matrix granules/tablets [2,3,8] as the sustained-release part of the formulation, and designed a single-unit dosage form including both an immediate-release part and a sustained-release part. The immediate-release part primarily reduces PBG, and the sustained-release part primarily reduces FBG. In the case of commercially available immediate-release nateglinide preparation (e.g. Fastic® tablets), nateglinide was released within 60 min in an *in vitro* dissolution test, and it was primarily PBG that decreased, with FBG not having decreased in healthy beagle dogs by 8 hours after administration [1,2,8,10].

Enteric-coated granules are coated with an anionic polymer as an enteric material, and show a pH-dependent release profile *in vitro*. Under acidic conditions, as the enteric material does not dissolve, almost none of the active ingredient is released. At neutral pH, on the other hand, the enteric material dissolves, and the active ingredient then starts to be released. Sustained release has been observed *in vivo* with administration of enteric-coated granules together with food [1,3,11-13].

Matrix granules/tablets consist of both an active ingredient and a matrix, such as a hydrophilic polymer, hydrophobic polymer, or lipid. The active ingredient disperses in a mesh structure composed of the matrix. The release is generally time-dependent [14], because the matrix dissolves

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sparingly and/or slowly, and the matrix structure then suppresses diffusion of the active ingredient from the preparation.

The above sustained-release part containing nateglinide reduced FBG from 9 to 12 hours *in vivo* [1,2,8], and when both an immediate-release part and a sustained-release part containing nateglinide were administered, both PBG and FBG were reduced. Similar studies have been reported by other research groups [15,16].These preparations are considered to be suitable for controlling PBG and FBG in a timely and precise manner.

Furthermore, with the objective of reducing the early-morning high blood glucose level, a retard-release preparation was investigated [17]. This preparation was designed using Pulsincap™ technology [18], and is composed of a water-insoluble capsule body that is filled with nateglinide, and sealed swellable hydrogel plug [17]. When the plug swells, nateglinide starts being released (retard release). This preparation was found to start to release nateglinide 4 hours after administration *in vivo* [17], and is expected to control early-morning high blood glucose level when taken just before the patient goes to bed.

Reducing Dosing Frequency

With the aim of reducing dosing frequency, many sustained-release oral preparations have been investigated. The principal release technology is matrix technology [19-32], and this is considered to be the reason why matrix preparations can be manufactured more easily than coated preparations. As mentioned above, one matrix preparation showed time-dependent release, and continuous control of blood glucose level was achieved, so reduction of dosing frequency is expected. Furthermore, there have been reports of unique dosage forms that are different from the above matrix technology, such as mucoadhesive microparticles [33] and osmotic tablets [34].

Mucoadhesive microparticles constitute a matrix preparation that contains an adhesive polymer as the matrix. After oral administration, the microparticles adhere to the digestive tract epithelium, especially in the stomach, and gradually release the active ingredient. This preparation is suitable for sustained release of anti-diabetic agents that are absorbed only in the upper intestine.

Each osmotic tablet consists of a semipermeable membrane shell, a core composed of an osmotically active ingredient, and a polymeric push compartment [35]. When the tablet absorbs water, the active ingredient dissolves inside the shell, and the polymeric push compartment expands, pushing the active ingredient out through the membrane shell. The release rate of the active ingredient from the tablet is constant (i.e. zero-order kinetics) [35]. There are hopes for important developments on the basis of this research in future.

Change of Administration Route to Improve Convenience

In general, the dosage form for medications for type-II diabetes mellitus is tablets, because these are easy for patients to take. However, a nasal preparation is considered preferable to an oral preparation because it can be taken easily without water. Elmowafy et al. [36]. have reported about a controlled-release, nasal preparation containing repaglinide [36,37]. This preparation consisted of microparticles (a matrix preparation) that were prepared by spray-drying, and consisted of repaglinide and polysaccharides [36,37]. It showed a time-dependent release profile *in vitro*. When administered nasally to male, Wister albino rats, this preparation reduced the blood glucose level over 24 hours [36,37], and it is expected to be more useful for diabetic patients than oral preparations.

Conclusion

Numerous controlled-release meglitinide preparations are currently being developed, for use as improved medications for type-II diabetes mellitus. If approved, it is hoped that they will help to increase quality of life for diabetic patients.

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