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Experimental Article

Poly-e-caprolactone-loaded miglitol microspheres for the treatment of type-2 diabetes mellitus using the response surface methodology

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الملخص

أهداف البحث: يهدف البحث لصياغة ووصف الكرات الدقيقة المحملة للميجليتول كنظام توزيع للدواء، ليتم تناوله عن طريق الفم، من أجل إطالة مدة مفعوله، ولتحقيق خفض الجرعات المتعددة. الميجليتول، هو دواء خافض لسكر الدم يؤخذ عن طريق الفم، ويتميز بقصر مدة التخلص منه، وهي ساعتين مع الحاجة لإعطائه بجرعات متعددة.

طرق البحث: استخدم تصميم وسيط كامل 3^2 لصياغة الكرات الدقيقة، باستخدام تقنية تبخر المذيبات. وتم فحص تأثير اثنين من المتغيرات المستقلة، وكمية البوليمر والتركيز السطحي على المتغيرات التابعة مثل تحميل الدواء وكفاءة التغليف إحصائيا باستخدام برامج مصممة خبيرة. كما تم تمييز الكرات الدقيقة باستخدام ماسح انبعاث المجال للمجهر الإليكتروني، والتحويل الفوري الطيفي للأشعة تحت الحمراء، وانكسار الأشعة السينية ثم تم تقييمها في المختبر لتحرير الدواء والاستقرار في الظروف المتسارعة.

النتائج: أظهر التقييم الإحصائي للتصميم نماذج تربيعية وخطية كنماذج هامة لتحميل الدواء وكفاءة التغليف. وتراوح حجم الجسيمات من ١٤٠-٥٤.٧ ميكرومتر وكانت كروية الشكل ذات سطح خشن. كما كانت كمية البوليمر عاملا هاما. وأكدت دراسة التحويل الفوري الطيفي للأشعة تحت الحمراء وانكسار الأشعة السينية توافق بوليمر الدواء. وتم العثور على تباطؤ معدل تحرير ميجليتول في المختبر من الكرات الدقيقة البوليمرية إلى مدة تصل ١٠ساعات.

الاستنتاجات: يمكن تركيب النموذج المطور أي — كابرولاكتون المتعدد الكرات الدقيقة المحمل للميجليتول بنجاح. ويمكن لهذه الكرات الدقيقة أن توفر نظاما واعدا لتوزيع متواصل للدواء لعلاج ارتفاع السكر بالدم المرتبط بالنوع ٢ لمرض السكري.

الكلمات المفتاحية: مرض السكري؛ الكرات الدقيقة؛ ميجليتول؛ منهجية استجابة سطحية؛ تبخر المذيبات

Abstract

Objectives: To formulate and characterize miglitol (MGL)-loaded microspheres as a drug delivery system for oral administration to prolong the duration of action for achieving reductions of multiple doses. MGL, an oral antihyperglycaemic agent, possesses a short elimination half-life of 2 h, so it must be administered in multiple doses.

Methods: A 3^2 full factorial design was employed for microsphere formulation using the solvent evaporation technique. The influences of two independent variables, the polymer and surfactant concentrations, on dependent variables, such as drug loading (DL) and the encapsulation efficiency (EE), were statistically investigated using Design Expert Software. Microspheres were characterized using field emission scanning electron microscopy (FE-SEM), Fourier transform infrared spectrophotometry (FTIR), and X-ray diffraction (XRD) and were evaluated for their *in vitro* drug release and stability at accelerated conditions.

Results: The statistical evaluation of the design showed quadratic and linear models as significant models for DL (R^2: 0.9932) and EE (R^2 0.9696). The sizes of particles ranged from 54.7 μm to 140 μm, and the particles were spherical in shape with coarse surfaces. The most significant factor was the polymer amount. FTIR and XRD studies confirmed the drug-polymer compatibility. *In vitro* release of MGL from polymeric microspheres was found to occur a slower rate of up to 10 h.

Conclusion: The developed poly-e-caprolactone-loaded MGL microspheres can be successfully formulated. These microspheres can provide a promising sustained release drug delivery system for the treatment of hyperglycaemia associated with type-2 diabetes mellitus.

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Keywords: Diabetes mellitus; Microspheres; Miglitol; Response surface methodology; Solvent evaporation

Introduction

Diabetes mellitus is a chronic disease that is increasing at an alarming rate around the world. Individuals with type-2 diabetes are increasing in number in every country; the disease affects major body systems, leading to serious problems such as kidney failure, lower limb amputation, heart disease, and stroke, and it is the seventh leading cause of death.[1,2] α-Glucosidase inhibitors can decrease postprandial plasma blood glucose levels by blocking oligosaccharide catabolism.[3,4]

Miglitol (MGL) is an α-glucosidase inhibitor used as oral antihyperglycaemic agent, and it is indicated for the treatment of patients with type-2 diabetes mellitus.[5] Chemically, it is (2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl) piperidine-3,4,5-triol. The dose is 25, 50 or 100 mg twice daily.[6,7] Several clinical studies have reported that MGL as monotherapy and in combination with other antidiabetic drugs is effective and ultimately reduces cardiovascular risk in cases of metabolic syndrome,[8,9,10–11] and doses of these agents can be adjusted accordingly.[12] The majority of adverse effects associated with MGL treatment involve disturbances of the gastrointestinal tract. Additionally, MGL has been reported to have a short elimination half-life (2 h),[13] requiring that it be administered in multiple doses daily; thus, there is an immense need to design and formulate new drug delivery systems that would effectively sustain the release of MGL, which would help to reduce the dosing frequency and adverse effects.

Various techniques have been reported for microsphere preparation; solvent evaporation techniques are very popular in the pharmaceutical industry due to their simplicity and cost-effectiveness. Microspheres can be effectively utilized as sustained drug delivery systems, ensuring drug release by maintaining therapeutic concentrations for prolonged periods of time.[14–17]

Poly-e-caprolactone (PCL), a biodegradable and biocompatible polymer, is ideally suitable for the controlled release of encapsulated drug over the long term.[18,19] PCL is relatively hydrophobic and does not swell significantly in aqueous medium, but its degradation includes a bulk erosion mechanism. Due to its *in vitro* stability, it has been used in sustained drug delivery applications.[20,21]

Response surface methodology (RSM) is a statistical and mathematical technique that has proved more advantageous than conventional experiments due to its minimum number of experimental runs.[22–24] However, no studies have been reported for the preparation of MGL microspheres using PCL applying a statistical design approach.

Our aim was to prepare sustained release MGL microspheres as a potential oral drug delivery system. Miglitol, a hydrophilic drug, was encapsulated using poly-e-caprolactone (PCL) polymer. Microspheres were formulated by applying 2 factors (polymer and surfactant amounts) at 3 levels (−1, 0, +1) to investigate their effects on drug loading and encapsulation efficiency. The microspheres were characterized for particle size, surface morphology, drug loading, encapsulation efficiency, and *in vitro* release behaviour.

Materials and Methods

Miglitol was provided by Glenmark Pharmaceuticals (Nashik, India) as a gift sample; poly-e-caprolactone (Mn ≈ 70,000–90,000 g/mol) and polyvinyl alcohol (PVA; Mn ≈ 125,000) were purchased from Sigma–Aldrich (USA) and Thomas Baker (Mumbai, India). Dichloromethane (DCM) was procured from Merck Specialties Private Limited (Mumbai, India). All of the other solvents and reagents in this work were of analytical/HPLC grade and were used as provided.

Factorial design

The design of experiment (DOE) extracted the maximum amount of information in a minimum number experimental runs. For the assessment and control of critical parameters, DOE is considered the most powerful technique.[25]

Various preliminary trials were conducted in accordance with varying drug, polymer and surfactant concentrations. Experimentally, the concentrations of PCL and PVA that yielded microspheres with optimum drug loading, encapsulation efficiency and *in vitro* release profiles were selected for the preparation of drug-loaded microspheres. The selected levels of PCL and PVA were used to generate a 3^2 full factorial (2-factor and 3-level) screening design, and 9 experimental runs were constructed using Design-Expert® Software. In the present study, the amount of polymer (X_1) and the amount of surfactant (X_2) were selected as independent variables (−1, 0, +1 levels) as shown in Table 1. The dependent variables were drug loading (Y_1) and encapsulation efficiency (Y_2). RSM was used to determine statistically the effects of the variables X_1 and X_2 on selected variables. Using this screening design, different models (linear, cross-product contribution [2FI] and quadratic and cubic model) were generated, and the significance of the model was determined by statistical parameters. Two-dimensional (2D) and three-dimensional (3D) response plots were constructed to study the main and interaction effects between factors and responses.

Preparation of MGL-PCL microspheres

MGL-PCL microspheres were prepared by the water-in-oil-in-water ($W_1/O/W_2$) double emulsion solvent evaporation technique.[26] Briefly, the drug (100 mg), predissolved in 2 ml of distilled water as an internal aqueous phase (W_1), was emulsified in a 10 ml solution of dichloromethane