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Original Article

Preparation and characterization of repaglinide loaded ethylcellulose nanoparticles by solvent diffusion technique using high pressure homogenizer

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ABSTRACT

Objective: An oral hypoglycemic agent repaglinide has less bioavailability and half-life. Its repeated dosing may cause side effects like headache, skeletal muscle pain and gastrointestinal effects. To overcome these problems, a sustained release nanoparticles has designed to maintain constant level of a drug in the patient's blood stream.

Materials and methods: The sustained released nanoparticles were prepared by Solvent emulsion diffusion technique using ethylcellulose as carrying material. Drug and polymer at different ratios were dissolved in ethyl acetate. To reduce size high pressure homogenizer was used. Final freeze dried nanoparticles used for characterization.

Results: The obtained nanoparticles sizes 90.48 nm, 148.4 nm, 240.7 nm were increased in order of polymer concentrations. There encapsulation efficiency was up to 97.66 ± 0.88% in higher drug-polymer ratio. Infrared spectroscopy proved that there was not interaction between repaglinide and ethylcellulose. X-ray diffraction observed the crystallinity of recovered nanoparticles was less than pure repaglinide. The obtained nanoparticles sustained 11.24 ± 0.06 to 18.32 ± 0.12% repaglinide up to 12 h. The mechanism of drug release was Anomalous/non-Fickian diffusion.

Conclusion: Saturated ethylcellulose ethyl acetate solution facilitates efficient encapsulation of repaglinide at 0.5% PVA. The drug release mechanism is combination of diffusion and erosion. This formulation can increase patient compliance by reduce the number of dosage and incidence of side effects.

1. Introduction

Type 2 diabetes mellitus is a complex metabolic disorder that involves a huge number of pathophysiologic mechanism, including insulin resistance, decreased insulin secretion, and excess glucose production by liver among others.[1] An oral hypoglycemic agent Repaglinide (REPA) is the first member of meglitinide class used in type 2 diabetes mellitus acts by binding to specific site on pancreatic β-cell and block ATP-dependent potassium channels to stimulate insulin release.[2]

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Due to its short half-life (<1 h) required frequent dosing before meal and this may cause side effects like headache, skeletal muscle pain and gastrointestinal effects.[3] To enhance the bioavailability and decrease the side effects of REPA, a sustained release new drug delivery system is necessitate. Solvent evaporation, solvent diffusion, solvent extraction or any modification in the basic principle of emulsification technique produces the drug loaded controlled release nanoparticles of desired properties.[4] Ethylcellulose (EC) is a non-biodegradable and biocompatible polymer which is extensively studied as encapsulating material for the controlled release of pharmaceuticals.[5,6] A comparative study by Ubrich et al concludes that EC was efficiently sustained drug for maximum time than other polymers like PLGA and polycaprolactone.[7] Therefore we selected EC as polymeric material for the preparation of repaglinide loaded ethylcellulose nanoparticles (REPA-EC NPs). The aim of present study was to formulate REPA-EC NPs by solvent diffusion technique and characterize it. The characterization includes particle size and zeta potential determination, encapsulation efficiency, drug content, surface morphology, drug–polymer interaction study by FTIR, comparative XRD, *in vitro* dissolution study and drug release kinetics determination by different models.

2. Materials and method

Repaglinide (REPA) was kind gift from Wockhardt Research Centre (Aurangabad, India). Ethylcellulose (300 cps viscosity grade) procured from Sigma–Aldrich USA. Ethyl acetate was purchased from Merck (Mumbai, India). Polyvinyl alcohol (PVA, MW Approx. 1,25,000) from SD Fine Chem Ltd. (Mumbai, India). The experimental work was performed by using triple distilled water filtered with 0.22 μ membrane filter.

2.1. Preparation of REPA-EC NPs

REPA-EC NPs were prepared by emulsion solvent diffusion technique.[4] Drug and polymer (1:2, 1:4, 1:6) were dissolved in ethyl acetate by using magnetic stirrer (Remi, India). This organic phase added drop by drop (2 ml/min) in external aqueous phase containing surfactant PVA in a fixed concentration (0.5% w/v) at 13,500 rpm (Omni GLH homogenizer). This suspension was then processed in high pressure homogenizer (Gea Niro Soavi, Italy) for eight cycles. A subsequently organic solvent from external aqueous phase was removed under reduced pressure. The formed REPA-EC polymeric nanoparticles were recovered by centrifugation (R243A, Remi) at 18,000 rpm for 20 min followed by washing thrice with distilled water and washed nanoparticles were subjected to freeze drying (Scanvac, Denmark).

2.2. Viscosity measurement

The viscosity of internal phase was measured by Brookfield rotational digital viscometer DVLV II at 25 °C.

2.3. Particle size and zeta potential determination

The obtained REPA-EC NPs were dispersed in distilled water by sonication and vortex mixing for 30 s and the particle size (Z-average mean) and zeta potential were determined by using Nano series Malvern Instruments, UK.

2.4. Percentage yield value of nanoparticles

The percentage yields of dried nanoparticles were calculated by using Eq. (1)

$$\text{Percentage yield} = \frac{\text{Mass of nanoparticles recovered}}{\text{Mass of polymers, drug and formulation excipients}} \times 100 \quad (1)$$

2.5. Encapsulation efficiency and drug content determination

Accurately weighed freeze dried nanoparticles were dissolved in dichloromethane. Then REPA was extracted in 50 ml phosphate buffer (pH 7.4) solution. After the evaporation of DCM and removal of precipitated polymer by filtration, the amount of drug in phosphate buffer was measured using Ultraviolet spectroscopy (U2900, Hitachi, Japan) at 275.5 nm. Encapsulation efficiency (%) and drug content (%, w/w) were represented by Eqs. (2) and (3) respectively.

$$\text{Encapsulation efficiency (EE \%)} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of drug used in formulations}} \times 100 \quad (2)$$

$$\text{Drug content}\left(\%, \frac{w}{w}\right) = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of nanoparticles recovered}} \times 100 \quad (3)$$

2.6. Field emission-scanning electron microscopy

The shape and surface characteristics of nanoparticles were investigated and photographed using Field Emission-Scanning Electron Microscopy (FE-SEM) (S4800, Hitachi, Japan). Appropriate samples were mounted on stub, using double sided adhesive carbon tapes. Samples were gold coated and observed for morphology, at acceleration voltage of 1.0 kV.

2.7. Fourier transform infrared spectroscopy

The samples (REPA, EC and nanoparticles) were homogeneously mixed with potassium bromide and infrared spectrums were recorded in region of 4000-400 cm^{-1} by using infrared spectrophotometer (IR-8400, Shimadzu Co. Ltd., Singapore).