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In vitro Evaluation of Novel Sustained Release Microspheres of Glipizide Prepared by the Emulsion Solvent Diffusion-Evaporation Method

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ABSTRACT

The objective of the current investigation is to reduce dosing frequency and improve patient compliance by designing and systematically evaluating sustained release microspheres of Glipizide. An anti-diabetic drug, Glipizide, is delivered through the microparticulate system using ethyl cellulose as the controlled release polymer. Microspheres were developed by the emulsion solvent diffusion-evaporation technique by using the modified ethanol,-dichloromethane co-solvent system. The polymer mixture of ethyl cellulose and Eudragit® S100 was used in different ratios (1:0, 1:1, 2:3, 1:4 and 0:1) to formulate batches F1 to F5. The resulting microspheres were evaluated for particle size, densities, flow properties, morphology, recovery yield, drug content, and *in vitro* drug release behavior. The formulated microspheres were discrete, spherical with relatively smooth surface, and with good flow properties. Among different formulations, the fabricated microspheres of batch F3 had shown the optimum percent drug encapsulation of microspheres and the sustained release of the Glipizide for about 12 h. Release pattern of Glipizide from microspheres of batch F3 followed Korsmeyers-peppas model and zero-order release kinetic model. The value of 'n' was found to be 0.960, which indicates that the drug release was followed by anomalous (non-fickian) diffusion. The data obtained thus suggest that a microparticulate system can be successfully designed for sustained delivery of Glipizide and to improve dosage form characteristics for easy formulation.

Key words: Microspheres, Glipizide, ethyl cellulose, Eudragit® S100, emulsion solvent diffusion-evaporation technique, sustained release

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INTRODUCTION

The limitations of the most obvious and trusted drug delivery techniques, such as conventional drug delivery system (DDS), have been recognized for some time now, the most important limitation of them being the patient incompliance due to frequent medication. This limitation can be overcome by modifying existing DDS. An appropriately designed sustained release (SR) or controlled release DDS can be a major step toward solving the problem associated with conventional DDS.[1,2] The SR DDS also have solutions for other limitations of the conventional DDS such as undesirable side effects due to fluctuating plasma drug level, inability to maintain adequate drug concentration in plasma for therapeutic effect, larger doses than those required by the cells have to be administered in order to achieve the therapeutic concentration, causing the undesirable, toxicological and immunological effects in non-target tissues.

Some drugs are readily absorbed from the GI tract, but easily eliminated from the body via excretion on account of its short half-life, requiring concomitant drug administration. Formulating an oral controlled release dosage form for these classes of drugs can be most beneficial as they release drug slowly in GIT and maintain constant drug levels in plasma for the extended period.[3] SR dosage forms, based on multiparticulate systems have attracted much attention due to their several benefits in reducing risk of dose dumping, and local irritation as the individual units can pass randomly through the pylorus and distribute widely in the GI tract[4] producing more predictable drug release profiles.

Glipizide is one of the most rapid and short acting second-generation blood-glucose-lowering drug belonging to class of sulphonylurea[5] and specially used in type II diabetes (non-insulin-dependent diabetes mellitus). The recommended dose range is 2.5-20 mg daily.[5] The absolute bioavailability is close to 1, thus it belongs to Biopharmaceutical Classification System (BCS) Class 2.[6] Gastrointestinal absorption of Glipizide is uniform, rapid, and essentially complete with relatively short elimination half life (3.4 ± 0.7 h).[7] The development of controlled release dosage forms thus, would clearly be advantageous. The characteristics of the drug such as short half life, low dose, and therapeutic use in chronic disease make it a suitable candidate for sustained release formulation.

The objective of the present invention is to develop and evaluate a sustained release microparticulate system of Glipizide in order to extend the drug release for about 12 h of duration and. The microspheres were evaluated for particle size, densities, flow properties, morphology, recovery yield, drug content, and *in vitro* drug release behavior.

MATERIALS AND METHODS

Materials

The active ingredient Glipizide was obtained as gift sample from Cipla Pharmaceuticals, Mumbai. Eudragit® S100 was procured from Evonik Degussa India Pvt. Ltd., Mumbai and Ethyl cellulose from Central Drug House (P) Ltd., New Delhi. Polyvinyl alcohol (PVA) was obtained from Research Lab., Mumbai. Ethanol, n-butanol, and dichloromethane used were of analytical grade purchased from S.D. Fine chemicals Limited, Mumbai, India. Double distilled water was used throughout the study.

Methods

Formulation of sustained release Glipizide microspheres

Before initiating formulation of microspheres, compatibility of Glipizide with different excipients was studied using the techniques like compatibility test for solid dosage form on lab scale[8] and DSC testing. Excipients used in formulation batches were found to be compatible with Glipizide.

Formulation of drug-loaded microspheres was carried out by the emulsion solvent diffusion-evaporation method. The polymers ethyl cellulose and Eudragit® S100 were used in different ratios with formulation batches F1 to F5, these ratios were shown in Table 1. The preferred ratio of 1:19 of Glipizide to polymer was used for all batches. Initially a solvent mixture of ethanol: dichloromethane: n-butanol was prepared in the ratio of 8:5:2 considering their volumes. An accurately weighed quantity of Glipizide (50 mg) and enteric polymer Eudragit® S100 along with ethyl cellulose was co-dissolved at room temperature in a solvent mixture. This solution was introduced into 1000 ml of 0.4% PVA aqueous solution at room temperature and dispersed to form emulsion at stirring rates of 200 rpm using a mechanical stirrer equipped with 4-blade propeller. Agitation provided by stirrer breaks the poured polymer solution to form an oil-in-water (O/W) type emulsion. This emulsion was then stirred for about 20 min at room temperature. After stirring, the solidified microspheres were recovered by filtration, washed with phosphate buffer (pH 7.4 ± 1) to remove all non-encapsulated drug, and further with distilled water to wash off PVA solution. Recovered microspheres were dried at 50°C for 12 h to remove solvents.

Evaluation of microspheres

Micromeritic properties

Microspheres were characterized for their micromeritic properties such as particle size, shape, bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. The size was measured using an optical microscope with the help of a calibrated ocular and stage micrometer,

Table 1: Formulae of Glipizide microspheres with variable polymer ratios

Formulation batches*#	Ratio of ethyl cellulose to Eudragit® S100	Quantity of polymer used (mg)		Quantity of Glipizide (mg)
		Ethyl cellulose	Eudragit® S100	
F1	1:0	950	0	50
F2	1:1	475	475	50
F3	2:3	380	570	50
F4	1:4	190	760	50
F5	0:1	0	950	50

*Stirring carried out at room temperature; #Ratio of solvent used in each formulation was 8:5:2 (Ethanol:DCM:n-butanol)