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PREPARATION AND EVALUATION OF ETHYL CELLULOSE MICROSPHERES OF PIOGLITAZONE HCl FOR SUSTAINED DRUG DELIVERY

Vankayalu Devendiran Sundar*, Nandhakumar Sathyamoorthy, Manam Madhuri, Magharla Dasaratha Dhanaraju

Research lab, GIET School of Pharmacy, NH-16 Chaitanya Knowledge City, Rajahmundry - 533 296, Andhra Pradesh, India

***Corresponding author e-mail:** sundarvd@yahoo.co.in

ABSTRACT

The objective of this study is to formulate and evaluate ethyl cellulose microspheres of pioglitazone hydrochloride for sustained/controlled drug release. Ethyl cellulose microspheres loaded with pioglitazone hydrochloride were prepared using emulsion solvent evaporation technique. The prepared microspheres were characterized for their average particle size, drug entrapment efficiency, scanning electron microscopy, DSC studies, in-vitro drug release behavior and in-vitro release mechanism. The microspheres were spherical with average particle size of 19 to 31 μm. The microspheres were free flowing smooth and spherical in shape with ideal surface morphology. The DSC endotherm proves the compatibility of drug and polymer. In-vitro release studies reveals that the microspheres formulation prepared with an increasing concentration of polymer exhibits more control release than the formulation prepared with lower concentration. Among all the batches, formulation with higher concentration of polymer shows an extended release and is suitable for formulate as sustained/controlled delivery system.

Key words: Pioglitazone hydrochloride, ethyl cellulose, solvent evaporation

INTRODUCTION

Controlled drug delivery systems are designed to deliver the drug in a predetermined manner for a specific period of time, locally or systemically. They offer numerous benefits over immediate release dosage forms in the treatment of chronic conditions by reducing the dosing frequency, increasing therapeutic benefit and reducing the side effects.[1,2] Microspheres constitute an important part of drug delivery system due to their small size and efficient carrier characteristics. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and having an ideal particle size less than 200 μm.[3] Microspheres can be defined as solid, approximately spherical particles ranging from 1 to 1000 μm, containing dispersed drug in either solution (or) microcrystalline form.[4] Polymer microspheres can be employed to deliver medication in a rate-controlled manner.[5]

Pioglitazone hydrochloride is a potent antidiabetic agent that acts primarily by decreasing insulin resistance in the management of type 2 diabetes mellitus.[6] Pioglitazone has short half life of 3-5 hr and so it is rapidly eliminated from the body. Inorder to maintain the therapeutic plasma concentration, repeated daily administrations are required. Drugs with biological half-life in the range of 2-8 hr have been suggested to be the good candidates for sustained release formulations.[7,8] Therefore controlled release formulations are needed for pioglitazone to minimize the risks and to improve the patient compliance. Ethyl cellulose is a non biodegradable, biocompatible, non-toxic and water insoluble polymer that has been widely used in the preparation of microspheres.[9] In present work, ethyl cellulose was selected as an encapsulating material for controlling the drug release rate. Oil in water (O/W) emulsion solvent evaporation method is the most common method used with microspheres which enables entrapment of wide range of hydrophobic

drugs.[4] The objective of this study is to formulate and evaluate ethyl cellulose microspheres of pioglitazone hydrochloride for controlled/sustained drug release.

MATERIALS AND METHODS

Pioglitazone hydrochloride was obtained from Cadila Care Ltd., Mumbai, as a gift sample. Ethyl cellulose was obtained from S.D. Fine chemicals limited, Mumbai. PVA was purchased from Merck limited, Mumbai. All other chemicals obtained were of analytical grade.

Preparation of Microspheres by solvent evaporation method: The microspheres were prepared by O/W emulsion-solvent evaporation technique.[4,10] The required amount of drug and polymer were dissolved in organic solvent mixture comprising chloroform and methanol in the ratio of 1:1 and emulsified with 40 ml of 1.0% aqueous PVA solution with the help of a high speed homogenizer at 5000 rpm. The formed emulsion was then stirred on a magnetic stirrer for 3 hr at 1000 rpm under room temperature to evaporate the organic phase. The microspheres so formed were washed with water, filtered and dried in an oven at 50^0 C. All formulations were stored in desiccators until use.

CHARACTERIZATION OF MICROSPHERES

Determination of Particle Size: Particle size of different batches of microspheres was determined by optical microscopy. The projected diameter of microspheres from each batch was determined using ocular micrometer and stage micrometer equipped with optical microscope. Analysis was carried out by observing the slide containing microspheres under the microscope.

Scanning Electron Microscopy (SEM) Analysis:
The shape and surface morphology of the pellets were examined with a scanning electron microscope (JOEL –JFC 5300). The pellets were mounted on an adhesion stuff and then coated with 30 nm layer of gold platinum under vacuum using an ion sputter coater (JOEL_JFC 1000E). The coated specimens were observed under the SEM at 15 kv and SEM micrographs were taken.

Drug entrapment efficiency: The amount of drug encapsulated in microspheres, was estimated by placing a weighed amount (50 mg) of microspheres into 50 ml of chloroform and methanol mixture and sonicated for 15 min in order to extract the entrapped drug completely. The solution was filtered through whatman filter paper. One ml of this solution was withdrawn and diluted to 50 ml with pH 7.4 phosphate buffer solution. The solution was assayed for drug content by UV spectrophotometer at 266 nm.

Encapsulation efficiency was calculated as:

EE (%) = (ED/AD) X 100

EE - Encapsulation efficiency
ED - Amount of encapsulated drug
AD - Amount of drug added

Differential scanning calorimetric (DSC) analysis: The physicochemical compatibilities of the optimized formulations were tested by differential scanning calorimetric (DSC) analysis. Thermal characterization of pure drug and microsphere formulation were performed with mettler Toledo, USA. About 10 mg of sample was placed in sealed aluminum pan. The equipment was calibrated with indium. The samples were scanned at 20^0 C/min from 50-400^0C.

Invitro Dissolution Studies: In vitro drug release studies were carried out for all batches in USP type II dissolution test apparatus at 100 rpm and the dissolution medium used is 900 ml of pH 7.4 phosphate buffer. Microspheres containing 100 mg of drug was used for dissolution study. Five ml of the aliquot was withdrawn at predetermined intervals. The required dilutions were made with pH 7.4 phosphate buffer and analyzed for the drug content spectrophotometrically at 266 nm against suitable blank. Equal volume of the dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition.

In vitro drug release kinetic studies: In order to study the exact mechanism of drug release from the microspheres, drug release data was analyzed according to zero order, first order and Higuchi square root model. The following plots were made: Qt vs t (zero order kinetic model); log (Qo-Qt) vs t (first order kinetic model); Qt vs square root of t (Higuchi model). Where Qt is the amount of drug released at time t and Qo is the initial amount of drug present in the microspheres. Plots were subjected to regression analysis to find out the regression coefficient and hence the order of release. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test.

RESULTS AND DISCUSSION

Particle size analysis: The mean particle size and size distribution of the ethyl cellulose microspheres of pioglitazone hydrochloride with different drug/polymer ratio were studied and found to be in

the range of **19 – 31 µm**. Increase in the concentration of polymer resulted in the increase in mean particle size. Higher concentration of polymer may lead to increased frequency of collisions, resulting in fusion of semi-particles and finally producing bigger particles thereby increasing the size of microspheres.[11,12]

Scanning Electron Microscopy (SEM) Analysis: The SEM photograph **(Fig 1-2)** revealed that the drug-loaded microspheres are spherical. Microsphere formulations containing higher amount of the polymer exhibits smoother surface than those prepared with lower amount of the polymer. Irregular surfaces were observed for those prepared with a lower amount of the polymer. This has greatly affected the morphological characteristics of the microspheres. As the drug-to-polymer ratio was increased, more spherical microspheres with smooth surfaces were obtained.

Drug entrapment efficiency: The results of encapsulation efficiency with drug: polymer ratio is shown in table I. Increase in the concentration of polymer resulted in the increased entrapment efficiency. The encapsulation was found to be good and around **66.8 to 82.5%** of the drug employed in the process was encapsulated. The percentage of encapsulation was higher **(82.5%)** in formulation-F5. This high encapsulation efficiency of a hydrophobic drug is due to its retention in the organic phase as the microspheres solidify which in turn due to high partition coefficient of the drug.[13]

Differential scanning calorimetric (DSC) analysis: DSC studies were performed on pure drug and for best formulation. The pure drug pioglitazone hydrochloride exhibit a sharp peak at 196^0 C presented in **fig 3**. The formulation doesn't exhibit a sharp peak at 196^0C. Hence it was observed that absence of endothermic peak of the drug at 196^0 C in the drug loaded microspheres indicate that the drug is uniformly distributed at molecular level in the microspheres.

Invitro Dissolution Studies: **Fig 4** explains the invitro drug release from ethyl cellulose microspheres which exhibits sustained release behaviour of formulations. The release profiles of formulations appear to be slow with negligible burst effect. The rate and amount of drug released was found to be decreased with increase in the concentration of the polymer. The formulations with lower levels of drug-to-polymer ratio exhibited higher initial burst in drug release. This could be attributed to the dissolution of drug present initially at the surface of the microspheres. However, the formulations showed little burst effect at higher drug-to-polymer ratio, ratifying better sustenance of drug released. Among the batches F1 to F5, a more controlled release was shown by F5 formulation, which releases 90.2% at the end of 10^{th} hour.

Drug release kinetics: Data obtained from invitro release studies was fitted to various kinetic equations and the nature of release of the drug from the formulations was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The highest correlation coefficient was found in Higuchi model which revealed that the drug release was diffusion controlled.

CONCLUSION

The microspheres of pioglitazone hydrochloride were prepared using drug: polymer ratio viz... 1:1, 1:1.5, 1:2, 1:2.5 and 1:3. The prepared microspheres were characterized for their drug entrapment efficiency, drug loading, particle size analysis, surface morphology, DSC studies, in vitro drug release behavior and in vitro release mechanism. Almost all the formulations showed fairly acceptable values for all the parameters evaluated. Among all the batches prepared Formulation F5 shows an extended release and is suitable to formulate as sustained/ controlled system. The release of drug from all the formulations followed diffusion controlled release followed by Higuchi which was confirmed by higher correlation coefficient values.

Table 1 – Drug /polymer ratio and physico-chemical properties of pioglitazone hydrochloride microspheres

Formulation batches	Drug	Polymer	Mean diameter* (µm)	Drug entrapment* (%)
F1	1	1:1.0	19.65	66.8
F2	1	1:1.5	21.50	69.2
F3	1	1:2.0	23.25	70.1
F4	1	1:2.5	28.05	76.4
F5	1	1:3.0	30.97	82.5

Average of three determinations.

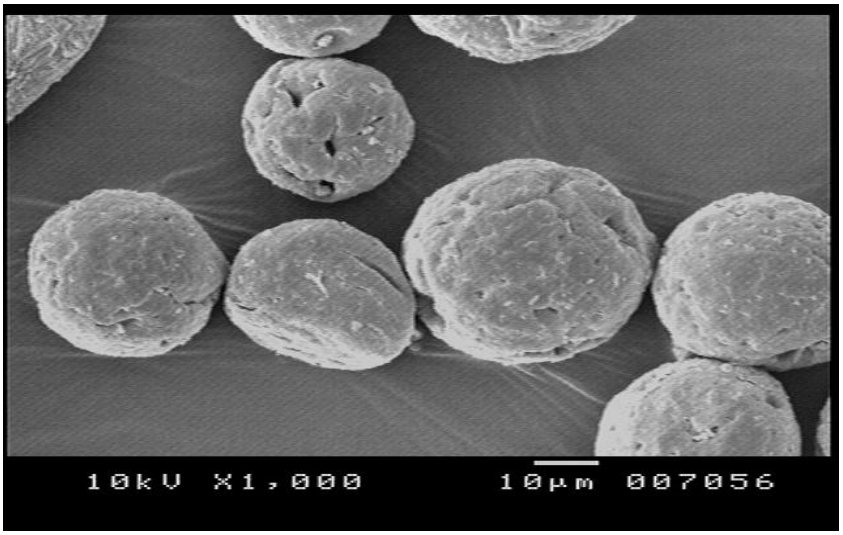

Fig 1: SEM photograph of Pioglitazone Hydrochloride microspheres formulated with lower concentration of ethyl cellulose.

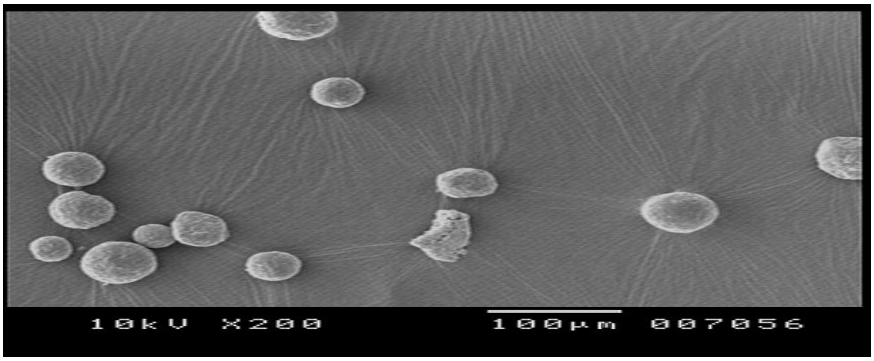

Fig 2: SEM photograph of Pioglitazone Hydrochloride microspheres formulated with higher concentration of ethylcellulose.

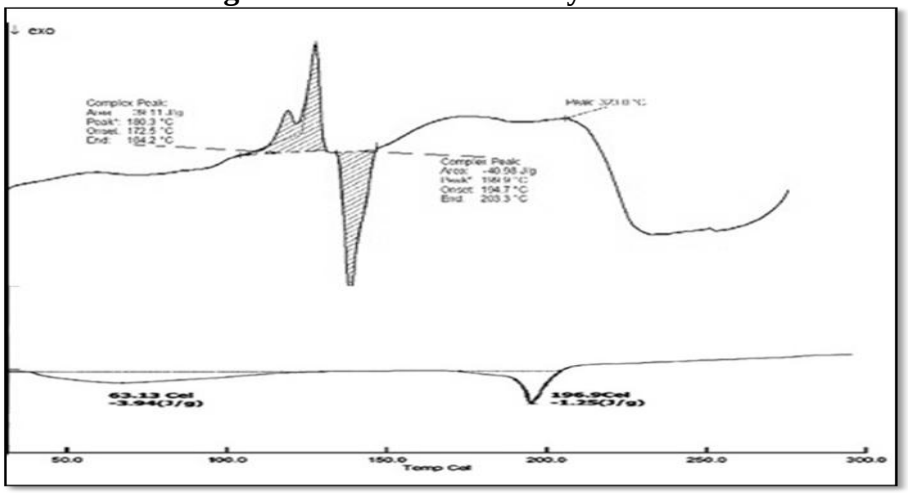

Fig 3: DSC thermo gram of microsphere formulation and pure pioglitazone hydrochloride.

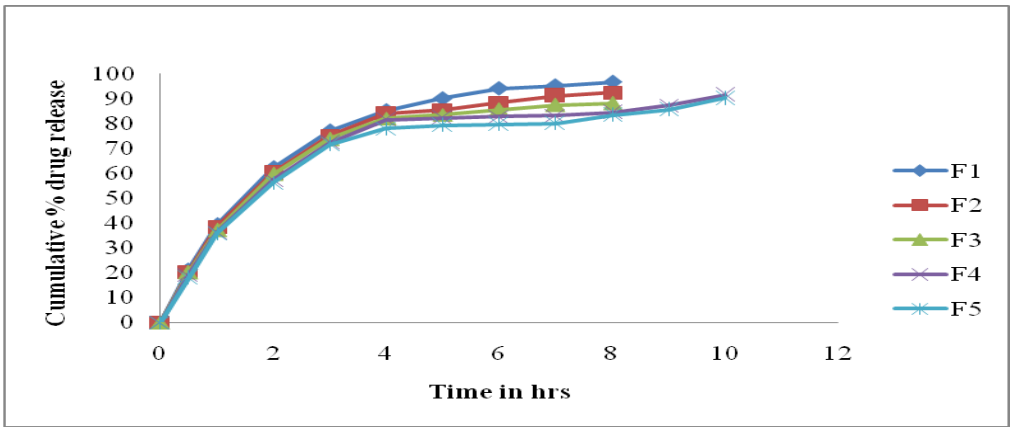

Fig 4: Invitro drug release study of microspheres of Pioglitazone hydrochloride

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