A REVIEW ON TECHNIQUES IMPLEMENTED IN FORMULATION OF FLOATING MICROSPHERES TABLETS OF GLIMEPIRIDE

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ABSTRACT

Glimepiride is an effective oral anti-diabetic agent that belongs to the second-generation sulfonylurea drug class and is widely prescribed in the management of non-insulin dependent (Type II) diabetes mellitus. It is poorly soluble in physiological fluids and is majorly absorbed from stomach. Dosage forms that are retained in the stomach would increase its oral bioavailability and efficacy. Glimepiride has a short biological half-life of 3-6 hrs and is eliminated rapidly. Now a days different techniques are available to enhance the solubility of drug like floating microsphere, solid dispersion of drug, liquisolid technique etc. One of the favourable strategy to improve the solubility and hence bioavailability of poorly water soluble drugs is the formulation of floating microsphere. So the floating microsphere tablet formulations are needed for glimepiride to prolong its duration of action and to increase its oral bioavailability and to improve patient compliance. This review article comprises of the research materialized in the field of formulation and evaluation of floating microsphere tablets of glimepiride.
INTRODUCTION

The use of oral antidiabetic drugs for the treatment of Type 2 diabetes is increasing rapidly. Glimepiride is an antidiabetic drug belongs to second generation sulphonylurea drug. It lowers the blood glucose level in patients with Type 2 diabetes (non-insulin dependent diabetes mellitus) by stimulating the release of insulin from the pancreatic $\beta$-cells. In this way it exerts a long-term effect of reducing the blood glucose levels. In addition, extra pancreatic effects may also play a role in the activity of glimepiride. It has low risk of hypoglycemia because of preservation of physiological suppression of insulin secretion in response to low blood glucose levels. It is completely (100%) absorbed following oral administration. It has rapid onset of action, 24 hr duration of effect with a half life of 5 hr and once a day dosing. A single daily dose of 1 mg has been shown to be effective, and the recommended maximal daily dose is 8 mg. It is completely metabolized by the liver to inactive products. The glimepiride belongs to Biopharmaceutical Classification System (BCS) class II having low solubility and high permeability. The drug shows low pH dependent solubility. It is practically insoluble in water, slightly soluble in methylene chloride (Dichloromethane) and very slightly soluble in methanol. It is soluble in DMSO (>10 mg/ml) and in ethanol (<1 mg/ml). In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37o C (<0.004 mg/ml). In media pH>7, solubility of drug is slightly increased to 0.02 mg/ml. The melting point of glimepiride is 207°C.[1]

Floating drug delivery systems (FDDS) or hydrodynamically balanced systems (HBS) are among the several approaches that have been developed to increase the gastric residence time of dosage forms. This Gastro retentive floating drug delivery system (GRFDDS) have a bulk density lower than that of gastric fluids and thus remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system.[2]

Microspheres are the carrier linked drug delivery system in which particle size ranges from (1-1000 $\mu$m) in diameter having a core of drug and entirely outer layers of polymers as coating material. Microspheres are sometimes referred to as microparticles. Microspheres are one of the novel drug delivery system which possess several applications and are made up of assorted polymers. They constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity. Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long period of time. However the success of these microspheres is limited due to their short
residence time at site of absorption. It would therefore be advantageous to have means for providing an intimate contact of the drug delivery system with absorbing gastric mucosal membranes. [3,4,5]

**PREPARATION OF MICROSPHERES**

The following techniques are used for the preparation of microspheres.

1. **Spray Drying technique**

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100μm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions this process is rapid and this leads to the formation of porous micro particles.[6]

2. **Wet Inversion Technique**

Chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyposphate through a nozzle. Microspheres formed were allowed to stand for 1 hr and cross linked with 5% ethylene glycol diglysidyl ether. Microspheres were then washed and freeze dried. Changing the pH of the coagulation medium could modify the pore structure of CS microspheres [7]

3. **Hot Melt Microencapsulation**

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e.g. poly anhydrides. Microspheres with diameter of 1-1000 μm can be obtained and the size distribution can be easily controlled by altering the stirring rate. [6]

4. **Single emulsion technique**

The microparticulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved/dispersed in aqueous
medium followed by dispersion in the non-aqueous medium e.g. oil. In the second step of preparation, cross-linking of dispersed globule is carried out. The cross linking is achieved by two methods i.e. either by heat or by means of chemical cross linking agents including glutaraldehyde, formaldehyde, acid chloride etc. [8]

5. Double emulsion technique
This process consumes formation of the multiple emulsions or the double emulsion of type w/o/w & is best suited to the water soluble drugs, peptides, proteins & the vaccines. The aqueous protein solution is dispersed in a lipophilic organic continuous phase which is generally consisted of polymer solution that eventually encapsulates protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenization before addition to aqueous solution of PVA. this results in formation of double emulsion which is then subjected to solvent removal by solvent evaporation maintaining the emulsion at reduced pressure or by stirring so that organic phase evaporates out. Examples: hydrophilic drugs like LHRH agonist, vaccines and proteins.[9]

6. Solvent Evaporation technique
The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The solvent Evaporation technique is The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelating prepared by complex coacervation were made disadvantage of this method is moderate temperature to which the drug is exposed [6]

7. Polymerization techniques
The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

I. Normal polymerization
II. Interfacial polymerization.

Both are carried out in liquid phase.

7.1 Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers. [10]

7.2 Interfacial polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed, one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase.[8]

8. Phase separation coacervation technique

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.[11]

9. Solvent extraction
Solvent evaporation method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for then microspheres. One variation of the process involve direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.[8]

REVIEW OF LITERATURE:

FLOATING MICROSPHERES TABLET OF GLIMEPIRIDE

Rangasamy Natarajan et al. 2014 formulated Glimepiride floating microspheres by Emulsion solvent diffusion evaporation technique. Accurately weighed amount of Glimepiride, ethyl cellulose and hydroxy propyl methyl cellulose K100M were dissolved in a mixture of dichloromethane (DCM): ethanol (ETN) (1:1) at room temperature. This solution was poured into 100ml distilled water containing 0.1% tween 80 maintained at a temperature of 30-40oC. The resultant emulsion was stirred with a propeller type agitator at 1200 rpm for 45 minutes to allow volatile solvent to evaporate. The resultant microspheres were filtered and dried. The ideal concentration of polymers were selected based on the in vitro drug release profile and desired time of 12 hrs. The in vitro drug release profile of glimepiride floating microspheres tablets containing hydroxy propyl methyl cellulose, ethyle cellulose in order to achieve the controlled release drug up to 12 hours.[2]

Ananya Parikibandla et al. 2014, prepared glimepiride microparticles using ethyl cellulose and combination of ethyl cellulose and Eudragit RS 100 and Eudragit RL 100 as the polymers by Emulsification (o/w) solvent evaporation method. Briefly Polymer was dissolved in 10ml of dichloromethane. To this 1mg of drug was added and mixed thoroughly. The above organic phase was added drop wise to 100ml of 1% Ethyl cellulose solution under magnetic stirrer at 800 rpm by keeping at 40’c and stirring is continued until total evaporation of DCM Then the solution was filtered and product was dried. Different formulations were prepared by taking different drug to polymer ratios of Eudragit RS 100 with Ethyl cellulose and combination of equal ratios of Eudragit RS 100, Eudragit RL 100 and Ethyl cellulose. The prepared particles were evaluated for particle size, encapsulation efficiency, Drug – polymer interaction by FTIR and in-vitro drug release. The glimepiride drug Formulation with combination of Ethyl cellulose Eudragit RS 100 and Eudragit RL 100 showed smooth surface and a good spherical shape. The percentage yield obtained in all the formulations was good and in the range of 59.25-94.44%. [12]
N. Sriram and R. Hima Bindu et al. 2013, employed emulsification (o/w) solvent evaporation method in the preparation of Glimepiride microspheres using ethyl cellulose and combination of ethyl cellulose and Eudragit RS 100 and Eudragit RL 100 as the polymers. Polymer was dissolved in 10ml of dichloromethane. To this 1mg of drug was added and mixed thoroughly. The above organic phase was added drop wise to 100ml of 1% PVA solution under magnetic stirrer at 800 rpm by keeping at 40˚c till the DCM evaporated. Different formulations were prepared by taking different drug to polymer ratios 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5 and 1:4 and 1:1, 1:2, 1:3 and 1:4 of Eudragit RS 100 with Ethyl cellulose and combination of equal ratios of Eudrajit RS 100, Eudrajit RL 100 and Ethyl cellulose. Formulation with combination of Ethyl cellulose Eudrajit RS 100 and Eudrajit RL 100 showed smooth surface and a good spherical shape. The in-vitro drug release studies showed that drug release was more in case of formulations containing both hydrophilic and hydrophobic polymers as compared to formulations only hydrophobic polymer. [13]

Sarath C Irisappan, et al. 2014, prepared Glimepiride microparticles by varying the drug and polymer ratios and by varying the surfactants emulsion solvent evaporation technique. Weighed amount of drug and polymer were dissolved in 10ml of acetone. The organic solution was then slowly added to 100ml of liquid paraffin containing 1% surfactant with constant stirring for 1hr. The resulting microparticles were separated by filtration and washed with petroleum ether. The microparticles finally air dried over a period of 12 hrs and stored in a dessicator. The angle of repose values of all the formulations were found to be in the range of 21.16 – 27.64, i.e. less than 30, which shows their free flowing nature of the prepared microparticles.[14]

C. Rubina Reichal et al. 2011, formulated glimepiride floating tablet to direct compressible blend using Glimepiride, Lactose monohydrate, Sodium bicarbonate, Hypromellose K4M CR or Hypromellose K100M CR, Carbopol 934P and Magnesium stearate as different grades of polymers. The homogenous blend was compressed into tablets on a single punch tablet press (Rimek mini press, India) equipped with7mm diameter standard concave punch and die. Compressed tablets of all the batches were circular in shape with no visible cracks. All the formulations showed reasonably good hardness value. Friability of the fabricated tablets was less than 0.5%w/w the results are presented in. The tablets of all the batches exhibited floating lag time less than 100 s. The tablets of Carbopol 934P batches more floating lag time compared to other batches. Tablets formulated with Carbopol 934P exhibited total floating time less than 7 h. This might be due to high affinity of Carbopol 934P toward water that promotes water penetration in tablet matrices leading to increased density.[15]
Muthusamy et al. 2014, prepared the microspheres of glimepiride by emulsification and evaporation method at 1200 rpm using ethylcellulose as a polymer dissolved in acetone and the powder of cross linked polyacrylic acid and the antibiotic amoxicillin were added and blended. The blend was dispersed in the light paraffin oil to form microsphere. Similar microsphere were prepared without using bioadhesive polymer as a control.[16]

REFERENCES


