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Preparation and Characterization of Mucoadhesive Microspheres Containing Antidiabetic Agent

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ABSTRACT

Diabetes mellitus is a heterogeneous disease of polygenic origin and involves insulin secretion and peripheral insulin resistance. Diabetes mellitus is the most common form of diabetes consisting 90% of the diabetic population. The number of diabetic patient in India is around 41 million. Majority of the conventional formulations available for some drawbacks, overcome the deficiency was made to formulate mucoadhesion of antidiabetic for the treatment of diabetes mellitus. Microspheres that are easily absorbed from the gastrointestinal tract and short half life are eliminated quickly from blood circulation and need frequent dosing. Carrier technology is an interesting and intelligent approach for the delivery of drug. Drug carrier particle like microspheres, mucoadhesive microspheres, nanoparticles, liposomes etc. The mucoadhesive microsphere is an important part of the particulate drug delivery system because of their small size and effective properties. Some drug delivery limitations was overcome by produced controlled drug delivery system which increase the therapeutic efficacy of a drug. Various approaches are used for the mucoadhesive microsphere as carrier system for drug delivery. Mucoadhesive microsphere was prolonged residence time at the site of action and good therapeutic efficacy of a drug. Mucoadhesive microspheres are an ideal targeting system with high safety margin.

INTRODUCTION

Microsphere are made from the naturally occurring biodegradable polymers they attracted considerable attention for several years in sustained drug delivery which precisely control the release rates and target drugs to specific body site with enormous impact in formulation and development of new drugs for novel drug delivery systems.[1]

Microspheres are important part of such delivery systems which may varied applications and be prepared using polymers. Microspheres are limited due to their short residence time at the site of absorption.[2] Drug action can be enhanced by developing new drug delivery system, such as a mucoadhesive microsphere drug delivery system. Drug delivery system remain in contact with the absorption tissue, releasing drug at the action site for increased bioavailability and both local and systemic effects.[3]

Drug administrated by the oral route consists the most convenient and preferred drug delivery to systemic circulation of the body. In this the most of the drugs are conventional dosage forms and short term limitations due to their inability to restrain at gastrointestinal tract.[4] It constitute an important part of particulate drug delivery systems by their small size and efficient carrier capacity. Advantages of mucoadhesive microspheres like increase bioavailability and absorption of the drugs and specific target of drugs to their site of action.[5]

Recently dosage form can precisely control the release rates and target the drug to a specific site. A special dosage form is needed for provide therapy and high margin of safety. Microspheres are formulated by techniques and polymers are characterized by evaluating preformulation and post-formulation parameters.[6]

Diabetes mellitus is the main cause of death in the world. Nowadays, 171 million people in the world with diabetes and this is increase to 366 million by 2030. The focus of the medical community for the prevention and treatment of the disease, and evident from the rising number of research papers every year on the subject.[7]

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, carbohydrates and proteins because of less ineffective use of the hormone insulin and less life expectancy and diminished quality of life.[8]

Mucoadhesion and microspheres

Mucoadhesion can be defined as the state in which two materials are formed, one material is biological in nature, are held together for a prolonged period by interfacial forces. In biological systems, mucoadhesion can be classified into three types.

- *Type 1*- mucoadhesion between two biological phases. For example wound healing.
- *Type 2*- bioadhesion of a biological phase to an artificial substrate. For example cell adhesion with culture dishes and biofilm formation on insects.
- *Type 3*- mucoadhesion of an artificial substrate to a biological substrate. For example adhesion of synthetic hydrogels to soft tissues.

Mucoadhesion is defined as the interaction between a mucin surface and a synthetic polymer. Mucoadhesion is promoted as a way of achieving site-specific drug delivery through the incorporation of mucoadhesive hydrophilic polymers within pharmaceutical formulations such as microspheres along with the active pharmaceutical ingredient.

Microspheres are defined as spherical particles and made up of polymer matrix in which therapeutic substance is dispersed through the matrix at the molecular. It is used for targeted and controlled release drug delivery and coupling of bioadhesive properties to microspheres has additional advantages e.g. specific targeting of drugs to the absorption site. Bioadhesive microspheres can be adhere to any mucosal tissue including those found in nasal cavity. Developing a mucoadhesive microsphere drug delivery system lies behind the fact that the formulation on a biological surface for localized drug delivery.[9]

Advantages of mucoadhesive microspheres

1 Formulation of mucoadhesive microsphere stay longer at the delivery site.

2 It allows bioadhesive molecules for targeting of particular site, for example gastrointestinal tract.

3 Residence time may be increased by combining with controlled active pharmaceutical ingredient for administration frequency.

4 Systemic delivery of dugs with first pass metabolism for greater bioavailability.

5 Less side effects and cost reduction may be achieved.

6 Good patient compliance, and convenience due to minimum frequent drug administration.

7 Uniform distribution of drug in the gastrointestinal tract which increases the drug administration.

8 Prolonged release of drug.

9 Maintain the concentration of therapeutic plasma drug concentration.

10 Less fluctuation in steady-state levels and better control of disease and less intensity of local and systemic side effects.[10]

Disadvantages of mucoadhesive microspheres

1 It may get modified when release from the formulation.

2 It may vary from a variety of factors like food and transit rate through gut.

3 Differences in the release rate are obtained from one dose to another.

4 In release pattern loss of integrity of the dosage form may lead to potential toxicity.

5 Dosage forms cannot be crushed or chewed.

Traditional non-specific first-generation mucoadhesive polymers

It may be divided into three main subparts:

1. Anionic polymers
2. Cationic polymers
3. Non ionic polymers.

Anionic and cationic polymers are shown to exhibit the greatest mucoadhesive strength. Such charged polymeric systems are now be explained in more depth.

- *Anionic polymers*

It is most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality. Such polymers are characterized by the presence of carboxyl and sulphate functional groups that give rise to a net overall negative charge at pH

values. Main examples include polyacrylic acid and sodium carboxymethylcellulose. These are excellent mucoadhesive property due to their formation of strong hydrogen bonding interactions. Polyacrylic acid derivatives have been studied as mucoadhesive platforms for drug delivery to the gastrointestinal tract. Polycarbophil is insoluble in aqueous solvent but high swelling capacity under neutral pH conditions and high levels of entanglement with mucus layer. Polymers are available in a wide range of molecular weights, easily modified gel networks, nontoxic and considered for oral use by the FDA.

- *Cationic polymers*

Cationic polymers are more extensively investigated within the current scientific literature. Chitosan is a cationic polysaccharide produced by the deacetylation of chitin. The properties of chitosan have been known for many years with many examples of its use in industry and medicine. Chitosan have been utilized as an antipathogenic and from an industrial investigation as a metal recovering agent. It has been noted for its film-forming properties and extensively in cosmetics. It has been employed as a dye binder for textiles and strengthening additive in paper and hypolipidic material in diets. Chitosan may provide improved drug delivery via a mucoadhesive mechanism and shown to enhance drug absorption. Chitosan is derived as the deacetylation of the naturally occurring insoluble precursor chitin. The major benefit of using chitosan within pharmaceutical applications which various chemical groups may be added in particular formation of novel polymers with added functionality. The properties of chitosan may be required of specific pharmaceutical technological challenges.

Novel second-generation mucoadhesive polymers

The major disadvantage in using traditional non-specific mucoadhesive systems is that adhesion may occur at sites. Surface carbohydrate and protein composition at potential target sites vary regionally and more accurate drug delivery.

1. *Lectins*

Lecithins are naturally occurring proteins that may role in biological recognition phenomena involving cells. For example, bacteria use lectins to attach themselves to the cells of the host organism. Lectins belong to a group of structurally diverse proteins and glycoproteins that can be specific carbohydrate residues. After mucosal cell-binding, lectins can either remain on the cell surface or receptor-mediated adhesion. Such systems can duality of function in

that lectin based platforms could not only allow targeted specific attachment and additionally offer a method of controlled drug delivery of pharmaceuticals via active cell-mediated. Lectins offer significant advantages concerning site targeting, many are toxic and the effects of repeated lectin exposure are largely unknown.

2. Thiolated polymers

Thiolated polymers are a type of second generation mucoadhesive derived from hydrophilic polymers like polyacrylates, chitosan and deacetylated gellan gum. Examples chitosan-iminothiolane, polyacrylic acid homocysteine and alginate cystein etc. The presence of thiol groups allows the formation of covalent bonds with cysteine rich sub-domains of the mucus gel layer and improved bioavailability.

Antidiabetic agents

Antidiabetic agents are help to control blood sugar level in people with diabetic mellitus. Antidiabetic drugs treat diabetes mellitus by reducing glucose level in the blood. Antidiabetic drugs are different classes and depends on the nature of diabetes, age of the person, and other factors. In the treatment protocol needs to be individualized and developed only type of diabetes has been categorized.[11]

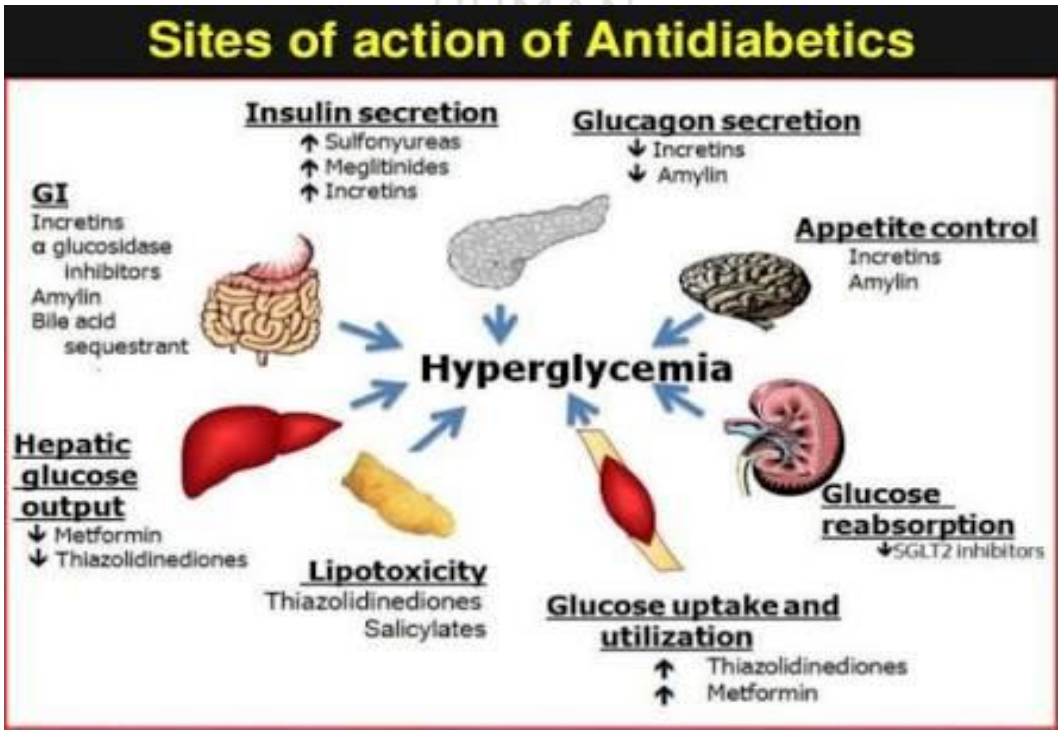

Fig.1 classification of antidiabetic agents

Classification of antidiabetic agents

- *Enhance insulin secretion*

1 *Sulphonylureas*– It is currently available in glipizide, glimepiride, glyburide and tolbutamide. Sulfonylureas provoke release of insulin from pancreases.

2 *Meglitinide analogues*- It is available in repaglinide, nateglinide.

It also releases of insulin from the pancreases. Administered before meal for control of post prandial hyperglycemia.

3 *Glucagon like peptide-1 receptor agonists* – It is available in exenatide, liraglutide.

It releases from pancreatic beta cells, and inhibits glucagon release from alpha cells, slows gastric emptying and suppress appetite.

4 *Dipeptidyl peptidase-4 inhibitors* – It is available in sitagliptin, vildagliptin.

In this rapid degradation of endogenous glucagon-like peptide-1, orally active inhibitors of dipeptidyl peptidase-4 developed as indirectly acting insulin secretagogues.[12]

- *Overcome insulin resistance*

1 *Biguanides*- metformin: Improve insulin-mediated glucose uptake and disposal in skeletal muscle and fat.

Adverse effects: lactic acidosis.

Phenformin higher risk of lactic acidosis that's why it may be banned in India since 2003.

2 *Thiazolidinediones*– pioglitazone: improved entry of glucose in muscle, and fat is improved.

- *Miscellaneous antidiabetic drugs*

1 Alpha-*glucosidase inhibitors*– acarbose, miglitol, voglibose.

These are the enzymes for the digestion of carbohydrates in small intestine mucosa. Discomfort for abdominal and loose stool are produced in near about 50% patients due to unabsorbed carbohydrates.

2 *Sodium-glucose co-transport-2 inhibitor* - dapagliflozin

Inhibition of sodium-glucose co-transport-2 induces glucosuria and less blood glucose in diabetic mellitus, and causes weight loss.[13]

Anti-diabetic drug name repaglinide

Description

Repaglinide ia a non-sulfonylurea insulin belonging to the melgitinide class. It is fast absorbed, rapid onset and short duration of action. It is metabolized in liver and excreted in the bile. It is taken with meal. Meglitinide is a neutral effect on weight. It appears to be more useful for lowering blood glucose.

Contraindication

Diabetic ketoacidosis, Type1 diabetes, co-administration with gemfibrozil, hypersensitivity to drug or inactive ingredients.

Pharmacodynamic

Insulin secretion by pancreatic beta cells are partly controlled by cellular membrane. Membrane is regulated through inverse relationship between the activity of cell membrane ATP sensitive potassium channel and extracellular glucose. Extracellular glucose enters the cell transporters. High concentrations of inhibit ATP-sensitive potassium channels causing membrane depolarization.

Mechanism of action

It lower blood glucose level by stimulating the release of insulin from the pancreas. This action depends on functioning beta cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes in low glucose concentrations. It closes ATP dependent in the beta cell membrane by binding.

Absorption

Oral administration repaglinide is fastly and completely absorbed from the gastrointestinal tract.

Toxicity

Headaches, diarrhea, constipation, muscle pain, upper respiratory infections.

Uses

It helps regulate the body's amount of glucose in blood. It is used in type2 diabetes. It helps prevent kidney damage.

Applications of mucoadhesive microspheres

1 The mucoadhesive microsphere is potential strategy for prolonged gastro residence time and improvement in contact with absorptive membrane to achieve good therapeutic performance of drugs.

2 It may improve drug delivery by various routes of administration like buccal, oral, and systemic or local effects.

3 It is used for targeting drug delivery system for various diseases and is involved in clinical as well as pharmaceutical aspects.

4 It may improve antigenicity by adjuvant action, modulation of antigen release, sand stabilization of antigen.

5 Reduced gastric irritation of drugs.

Methods

- *Emulsion cross linking method*

This method is functional group of polymers to crosslink with aldehyde. In this method, a water-in-oil emulsion is prepared by emulsifying aqueous solution in the oily phase. Aqueous droplets are stabilized by using surfactant or dioctyl sodium sulphosuccinate. Microspheres are filtered and washed repeatedly with petroleum ether to remove of oil. Finally washed with water and then dried at room temperature.[14]

- *Ionotropic gelation*

This method is formed by dissolving the gel-type polymers, like alginate, aqueous solution by suspending the active ingredient in the mixture of solution through needle to produce micro

droplets which fall into a hardening solution. Calcium ions are present in the hardening solution for forming gelled microspheres.[15]

- *Phase inversion method*

This method involves addition of drug by dilute polymeric solution, with methylene chloride; and resultant mixture is poured in unstirred bath of non-solvent, petroleum ether. Microspheres are produced, washed with petroleum ether and then dried.[16]

- *Spray drying*

In this the polymer is firstly dissolved in a volatile organic solvent like acetone. The drug in the solid form and then dispersed in the polymer solution. This dispersion is atomized in a stream of hot air. Formation of the small droplets in which solvent evaporates instantaneously and formation of the microspheres. Microparticles are separated from the hot air by cyclone separator while the solvent is removed by vacuum drying. Major advantage of process is feasibility of operating under aseptic condition. This process is rapid and the formation of porous microspherers.[17]

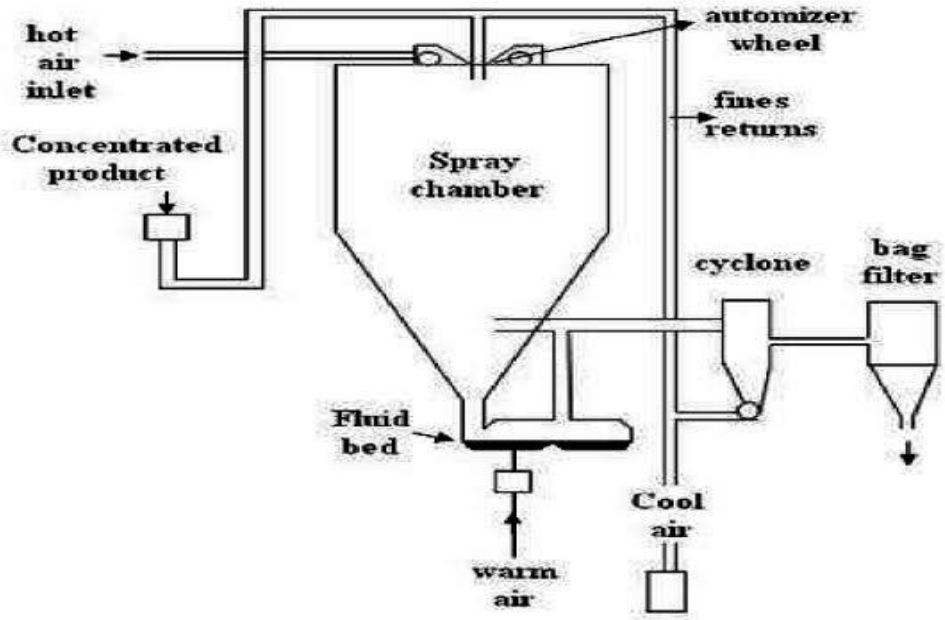

Fig. 2 Spray drying method.

- *Solvent removal method*

In this method non-aqueous microencapsulation are suitable for water liable polymers like polyanhydrides. In this method drug was dissolved in a volatile organic solvent methylene chloride. This mixture was suspended in silicone oil and methyl chloride. Pouring the polymer solution into silicone oil and petroleum ether was added and stirred. Then microspheres are dried under a vacuum.[18]

- *Solvent evaporation method*

In this method a specified amount of polymer was solubilized in a fixed amount of polymer was solubilized in acetone. The drug was dispersed in a polymer solution. The mixture was added to a continuous phase which contains span80 as an emulsifier. The dispersion was agitated continuously in beaker by a mechanical stirrer. The liquid was stirred till 45 min until acetone was evaporated completely. After emulsification, the settled particles were separated out by filtration. The batch of solidified microparticles was washed five times with n-hexane and dried at room temperature for 24h.[19]

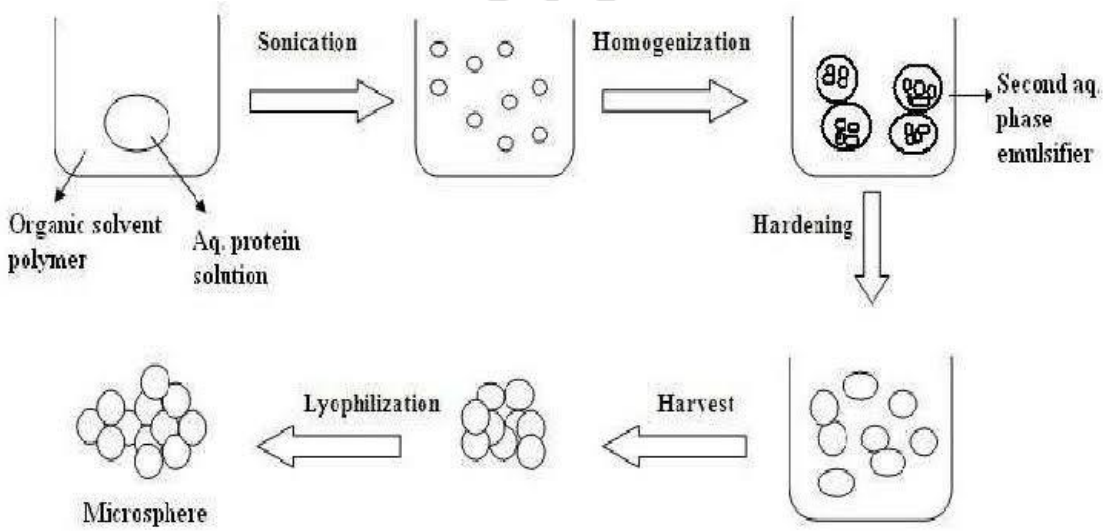

Fig. 3 Solvent evaporation method.

Characterization of mucoadhesive microsphere

1. *Particle size analysis*

The particle size of the microspheres are determined by optical microscopy. The eye piece micrometer is calibrated with the help of a stage micrometer for selected samples of all the formulations.[20]

2. Shape and surface morphology

The shape and surface characteristics of the microspheres are evaluated by scanning electron microscopy.[21]

3. Bulk density

The microspheres are weighed and transferred to a glass graduated cylinder. The cylinder is tapped until the microsphere bed volume is stabilized. The bulk density is established by the ratio of microsphere weight the final volume of the microsphere.[22]

4. Density determination

Density of the microspheres can be measured by multi volume pychnometer. Weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber, results in a decrease in pressure within the chamber.[23]

5. Stability studies

Microspheres are stored in the following conditions:-

Ambient humid condition.

Room temperature.

Refrigerator 5^0C-8^0C.[24]

6. Scanning electron microscopy

Scanning electron microscopy of the microspheres show surface morphology of the microspheres like shape and size.[25] In this method microspheres are mounted directly on the scanning electron microscopy with the help of double-sided sticking tape and coated with gold film under pressure.[26]

7. Angle of contact

The angle of contact is determined by the wetting property of a microparticulate carrier. It determines the nature of microspheres in terms of hydrophilicity.[27] Thermodynamic property is specific to solid by the presence of the adsorbed component. The angle of contact is measured at the solid interface.[28]

CONCLUSION

Mucoadhesive microspheres are drug delivery system that have a lot of interest of different researchers and scholars because of their advantage of controlled and sustained release of action as a drug carrier. It maintains the effect of plasma concentration over prolonged action of drug release. It will increase the residence time of the drug. Mucoadhesive delivery of drug is promising the area of systemic delivery of orally inefficient drug in attraction alternative for noninvasive delivery of potent peptide and protein drug molecules. Drug content may be found uniform in a batch of mucoadhesive microspheres. microsphere drug delivery system for designing controlled and delayed release of oral formulations. Microspheres are targeting drug delivery system with safety profiles.

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