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A review on microspheres as drug delivery carriers for management of diabetes mellitus

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Abstract

Diabetes mellitus is a metabolic disorder, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Type 2 diabetes mellitus is a heterogeneous disease of polygenic basis and involves both defective insulin secretion and peripheral insulin resistance. Although the availability of new agents for treatment of type 2 diabetes mellitus, oral hypoglycemic are base of therapy, because they are relatively economical and well tolerated. Aim of designing controlled drug delivery system, is to ensure the safety and to improve efficiency of drug as well as patient compliance. This is achieved by better control over plasma drug level. A well designed controlled drug delivery system can overcome some of the inconvenience of conventional therapy and enhance the therapeutic efficacy of a given drug. Controlled drug delivery occurs when a polymer, whether natural or synthetic, is prudently combined with a drug or other active agent in such a manner that the active agent is released from the material in a predesigned mode. Microspheres form an essential part of novel drug delivery systems. Microspheres are usually free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and preferably having a particle size less than 200 µm. Microspheres reduce the dosing frequency and improve patient compliance by designing and evaluating Sustained Release microspheres for effective control of diabetes. A controlled release system designed to increase its residence time in the stomach with contact with the mucosa. Microsphere carrier systems made by using various polymers and prepared by different techniques. The objective of the present review is to compile the various polymer loaded microspheres of oral hypoglycemic for treatment of type 2 diabetes mellitus.

Key-Words: Microspheres, Diabetes type-2, Controlled drug delivery, Carbopol, HPMC

Introduction

Diabetes (Diabetes mellitus) is classed as a metabolism disorder. Metabolism refers to the way our bodies use digested food for energy and growth, what we eat is broken down into glucose. Glucose is a form of sugar in the blood and it is the principal source of fuel for human body. When food is digested the glucose makes its way into bloodstream, our cells use the glucose for energy and growth. However, glucose cannot enter our cells without insulin being present, insulin makes it possible for our cells to take in the glucose. Insulin is a hormone that is produced by the pancreas. After eating, the pancreas automatically releases an adequate quantity of insulin to move the glucose present in our blood into the cells, and lowers the blood sugar level.

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A person with diabetes has a condition in which the quantity of glucose in the blood is too elevated (hyperglycemia). This is because the body either, does not produce enough insulin, produces no insulin, or has cells that do not respond properly to the insulin the pancreas produces. This results in too much glucose building up in the blood. This excess blood glucose eventually passes out of the body in urine. So, even though the blood has plenty of glucose, the cells are not getting it for their essential energy and growth requirements. It is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment,

death. The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease. [1-3]

Type 1

Type 1 indicates the processes of beta–cell destruction that may ultimately lead to diabetes mellitus in which "insulin is required for survival" to prevent the development of ketoacidosis, coma and death. Type 1 is usually characterized by the presence of anti–GAD, islet cell or insulin antibodies which identify the autoimmune processes that lead to beta–cell destruction.

Type 2

Type 2 is the most common form of diabetes and is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that this form of diabetes is clinically manifest. By definition, the specific reasons for the development of these abnormalities are not yet known.

Other specific types

Other specific types are currently less common causes of diabetes mellitus, but are those in which the underlying defect or disease process can be identified in a relatively specific manner. They include, for example, fibrocalculous pancreatopathy, a form of diabetes which was formerly classified as one type of malnutrition–related diabetes mellitus. [1 2 3]

Treatment strategies for management diabetes mellitus

1. Type 1 diabetes is invariably treated with insulin.
2. Type 2 diabetes is often allied with obesity. Serum insulin levels are normal or elevated, so this is a disease of insulin resistance. Type 2 is frequently treated by oral hypoglycemic.

Table1. Review on Oral hypoglycemics [1 2 3 5]

Oral Antidiabetics	Mechanism of Action	Side Effects
Sulfonylureas Glyburide Glyburide micronized Glimiperide Glipizide Glipizide-gits Tolbutamide Chlorpropamide Tolazamide Acetoheximide	Stimulate first-phase insulin secretion by blocking K+ channel in ß-cells	Late hyperinsulinemia and hypoglycemia Weight gain
Biguanides Metformin	Decrease hepatic glucose production	Nausea, Diarrhea
Metformin-XR	Increase muscle glucose uptake and utilization	Anorexia, Lactic acidosis
Meglitinides Repaglinide Nateglinide	Stimulate first-phase insulin secretion by blocking K+ channel in ß-cells	Hypoglycemia Weight gain
Thiazolidinediones Rosiglitazone Pioglitazone	Increase insulin sensitivity via activation of PPAR-g receptors	Fluid retention and weight gain
a-Glucoside Inhibitors Acarbose Miglitol	Decrease hepatic glucose production Delays glucose absorption	Flatulence Abdominal bloating

Novel drug delivery system for management of Diabetes Mellitus

Microsphere as a drug delivery systems are considered as a suitable means to deliver the drug to the target site with specificity and to maintain the desired concentration at the site of interested area without side effects. Microspheres are also referred as microparticles. Microspheres are characteristically free flowing powders. Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable for several years in sustained drug delivery. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release. Microspheres are small and have large surface to volume ratio. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are tremendously important, frequently dictating activity. [4-6]

Advantages of microspheres [14]

- Increase bioavailability
- Alter the drug release & separation of reactive core from other materials.
- Improve the patient's compliance
- Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
- Reduce the reactivity of the core in relation to the outside environment.
- The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.

- Decrease evaporation rate of the volatile core material.
- Convert liquid to solid form & to mask the bitter taste.
- Protects the GIT from irritant effects of the drug.
- Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
- Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections. [5 6]

Components

A number of different substances both biodegradable as well as non biodegradable have been investigated for the preparation of microsphere.

Core material

- Drug or active constituent
- Additives like diluent
- Stabilizers
- Release rate enhancers or retardants

Vehicle

1. Aqueous 2. Non Aqueous

Polymers

Types of polymer	**Types of natural polymer**	**Examples**
1.Natural polymer	a)Proteins	Albumin, Gelatin, and Collagen
	b)Carbohydrates	Agarose, Carrageenan, Chitosan, Starch
	c)Chemically modified Carbohydrates	Poly dextran, Poly starch. [3]
2.Synthetic polymer	**Types of synthetic polymer**	**Examples**
	a. Non-biodegradable	1.)Poly methyl methacrylate (PMMA) 2.) Acrolein 3.) Epoxy polymer
	b. Biodegradable polymers	1) Lactides 2) Glycolides & their co polymers, 3) Poly alkyl cyano acrylates

Coating material

- Inert polymer
- Plasticizer
- Coloring agent
- Gelatin, gum Arabica, methyl cellulose, beeswax, carnauba wax

Methods of preparation of microsphere [12 13 14]

1) Single Emulsion Technique:-

Microspheres of natural polymers e.g. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. The cross linking can be achieve by cross linkers. [7, 8]

2) Double Emulsion Technique:-

This method involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is most appropriate to water soluble drugs, peptides, proteins and the vaccines. Both the natural as well as synthetic polymesr can be used. The aqueous active constituent's solution is dispersed in a lipophilic organic continuous phase. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the active constituents contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonic.ation before addition to the aqueous solution. This consequences formation of a double emulsion. [7, 8]

3) Polymerization Techniques:-

The polymerization techniques of microspheres preparation are mainly classified as:

a. Normal polymerization

b. Interfacial polymerization.

a) 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.

b) Interfacial polymerization:

Reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer.

4) Phase Separation and Coacervation:-

This method is particularly designed for preparing the reservoir type of the system, i.e. to encapsulate water soluble drugs. However, some of the preparations are of matrix type, when the drug is hydrophobic in nature. The principle of process is based on the decreasing the solubility of the polymer.

5) Spray Drying And Congealing:-

These methods are based on the drying of the mist of the polymer and drug in the air. On the basis of the cooling of the solution and removal of the solvent , these two processes are named respectively. Atomization lead to the formation of small droplets from which the solvent evaporates leads to formation of microspheres in a size range 1-100µm. Microspheres are than separated from the hot air by means of the cyclone separator and the solvent are removed by vacuum drying. [7, 8]

6) Solvent Extraction:-

This method is used for the preparation of microparticles, involves the removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvent and organic phase is removed by extraction with water. The process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug. Solvent removal rate depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer. [7, 8]

Characterization [13 14 15]

1.Morphology

All batches of microspheres should be studied for shape and size for uniform distribution. Particle size and shape of micro particles are obtained by various techniques.

a. Scanning electron microscopy (SEM)

The microsphere shape and surface characteristic are generally evaluated by scanning electron microscopy (SEM). The observations are made with a scanning electron microscope. The samples are mounted directly onto the SEM sample holder using double-sided sticking tape and images are generally recorded at the required magnification.

b. Energy dispersive X-ray spectrometry (EDS)

The elemental analysis of the microsphere is determined by energy dispersive X-ray spectrometry after the procedure. The X-ray spectrum is conducted with 10 keV. The X-ray spectrum is then used for semi-quantitative analysis.

2. Particle size analysis

Particle size and size distribution of microspheres is usually by the laser light scattering. The dispersion of microspheres was added to the sample dispersion unit and stirred in order to reduce the aggregation between the microspheres

3. Swelling studies

It is determined only for mucoadhesive microsphere. Water uptake of the microspheres is determined by measuring the extent of swelling of the matrix in particular solvent. To ensure complete equilibration, microspheres were allowed to swell for particular time. The excess surface adhered liquid drops were removed by blotting with soft tissue papers and the swollen microspheres were weighed to an accuracy of 0.01mg. The microspheres were then dried in an oven at until there was no change in the dried mass of the microspheres. The % equilibrium water uptake was calculated as:

% Water uptake= Weight of swollen microspheres−Weight of dry microsphere / Weight of dry microspheres×100.

4. Density determination:

Density of the protinons microspheres can be measured by using a multi volume pychnometer. Accurately weighed sample in a cup is placed into the multi volume pychnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. Expansion results in a decrease in pressure. Two consecutive readings of reduction in pressure at different initial pressure are noted and the density of the microsphere carrier is determined.

5. Isoelectric point:

Microelectrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different pH values is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behaviour of the microspheres.

6. Capture efficiency/ percent entrapment:

Capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyses. The lysate is then placed to the determination of active constituents. The percent encapsulation efficiency is calculated using following equation:

% Entrapment = Actual content/Theoretical content x 100

7. Angle of response:

The angle of contact is to determine the wetting property of a micro particulate carrier. It shows the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is particular to solid and affected by the existence of the adsorbed component. The angle of contact is measured at the solid/air/water interface.

8. In vitro methods

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of in vitro and in vivo techniques have been reported. In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physicochemically and hydrodynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of in vitro release methods for buccal formulations; however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed.

Beaker method:

The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.

Interface diffusion system

This method is developed by Dearden & Tomlinson. It consists of four compartments. The compartment A represents the oral cavity, and initially contained an appropriate concentration of drug in a buffer. The compartment B representing the buccal membrane, contained 1-octanol, and compartment C representing body fluids, contained 0.2 M HCl. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned to compartment A with a syringe.

Modified Keshary Chien Cell:

A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50ml) at 37˚C as dissolution medium

Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using both rotating elements, paddle25, 26, 27 and basket. Dissolution medium used for the study varied from 100- 500 ml and speed of rotation from 50-100 rpm.

9. Buccal Absorption Test

Used for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrates at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However the most widely used methods include *in vivo* studies using animal models, buccal absorption test.

Pharmaceutical applications of microspheres [11 12]

- Gene therapy with DNA plasmids and also delivery of insulin.
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control..
- Tumour targeting with doxorubicin and also treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used in isolation of antibodies, cell separation, and toxin extraction by affinity chromatography. As Monoclonal antibodies are extremely specific molecules, this extreme specificity of monoclonal antibodies can be utilized to target these microspheres to selected site.
- Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra arterial/ intravenous application.
- Release of proteins, hormones and peptides over extended period of time.

Applications of microspheres[8 9 10]

New applications for microspheres are discovered every day, below are just a few:

Type of microsphre	Applications
Radioactive Microspheres	Radioembolization of liver and spleen tumors, Local radiotherapy, Local restenosis prevention in coronary arteries.

Fluorescent Microspheres	Blood flow determination, tracing, *in vivo* imaging and calibration of imaging .
Hollow microspheres	Used to decrease material density.
Monodispere microspheres	Calibrate particle sieves, and particle counting apparatus.
Ceramics microspheres	Paints and powder coatings.
Magnetic microspheres	They are use for drug targeting. Magnetic fluid hyperthermia. Improvement in drug release.

Table 2: Review on various oral hypoglycemic microspheres. [27 28 29 30 31]

Drug	Polymer	Method used for preparation
Glipizide	Sodium alginate	An orifice-ionic gelation process
	Carbopol 971	
	Chitosan	Simple emulsification phase separation technique
Metformin hydrochloride	Ethyl cellulose	Non-aqueous Solvent evaporation method
	Sodium carboxy methyl cellulose	
	carbopol	Emulsification solvent evaporation
	Hydroxyl propyl methyl cellulose k4m (hpmc)	
	Eudragit rs100	
Repaglinide	Chitosan	Solvent evaporation method
	Eudragit rs-100	
Rosiglitazone	Sodium carboxy methylcellulose	Emulsification Solvent evaporation method
	Carbopol 934	
Pioglitazone Hcl	Sodium alginate	Orifice ionic gelation method
	Carbopol 934	
	Carbopol 971	
	Carbopol 974	
	Polycarbophi	
	HPMC K100 M	

Conclusion

Control release of drug profile has been a major aim of pharmaceutical research. Control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with better therapeutic possibilities and substantial benefits for patients. Microspheres would become the promising candidate for delivery various drugs in sustained release manner. Dosing frequency and loss of drug also reduced by use of such type of formulations. Consequently various polymeric microspheres would become a promising candidate for therapy of diabetes type-II in the future and in managing diabetes. To achieve controlled release of drug as well as to enhance bioavailability or for drug targeting to specific areas of body microspheres are designed.

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