An Overview on Polymeric Nanoparticles used in the treatment of Diabetes Mellitus

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ABSTRACT

The review was carried out to discuss in detail about the polymeric nanoparticles for diabetic treatment. The diabetes is the chronic metabolic disorder characterized by the deficiency of insulin production. The various treatments are available for the diabetes and the nanoparticles are having the several advantages. The various types of nanoparticles are available for the anti-diabetic drugs; the polymeric nanoparticles are the one of the most commonly used nanoparticles. The polymeric nanoparticles are commonly 10-1000nm in size. The polymeric nanoparticles are formulated by drug with the polymers. The main advantages of the polymeric nanoparticles are the simplest preparation method, targeted delivery, the minimizing of the dose and high therapeutic efficiency. In this review was mainly can be focused on advantages, disadvantages of polymeric nanoparticles, various polymers, various formulation techniques, diabetes disease profile, insulin production, various anti-diabetic drugs and the polymeric nanoparticle formulation of anti-diabetic drugs.

Key words: anti-diabetic, insulin, polymeric nanoparticles, polymers, hypoglycemic drugs, metformin, glipizide

INTRODUCTION

Nanomedicine is a subdivision of nanotechnology, which uses small particles that are more than 10 million times smaller than the human body. In nano-medicine, these particles are greatly lesser than the living cell. Because of this, nanomedicine presents many innovative chances in the fight against all types of cancer, neurodegenerative disorders and other diseases. (SovanLal *et al*., 2011)

Liposomes are concentric bilayered vesicles in which an aqueous volume is completely surrounded by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Nanocrystals are aggregates of about hundreds or thousands of particles that combine in a crystal-like form, composed of pure drug with only a thin coating comprised of surfactant or combination of surfactants.(Nishikant *et al*., 2012, Senthilnathan *et al*., 2016) Solid Lipid Nanoparticles contain a solid lipid medium, where the drug is normally incorporated, with an average diameter below 1 µm. (Nagarajan *et al*., 2015) Dendrimers, an exceptional class of polymers, are extremely branched macromolecules whose size and shape can be exactly measured. Metallic nanoparticles are the having the metallic compounds like gold, silver, selenium, iron etc. the green synthesized nanoparticles are having the plant source of nanoparticles. (Nagavarma *et al*., 2012, Mohanraj *et al*., 2006)

Polymeric nanoparticles are commonly 10-1000nm in dimension. These polymeric nanoparticles are formulated from the polymers, which have the nature of bio-adaptability, bio-comptability and bio-degradable. The drug is dissolved, entrapped, encapsulated to a nanoparticle medium. The nanoparticles, nano-spheres or nano-capsules are obtained by depending up on the preparation. In nano-capsule system, the drug is limited to a cavity enclosed by even polymer layer, while the nano-shell contains of medium, in which the drug is physically and uniformly dispersed.(Konwar *et al*., 2013, Neha *et al*., 2013)

Advantages of polymeric nanoparticles

- Preparation method is easy

- Targeted drug delivery method
- Because of their lesser size Nanoparticles enter small capillary and are taken up through the cell which allows for well-organized drug buildup at the target sites in the body. (Nishikant *et al*., 2012)
- Good control of over size and size distribution.
- Good protection of the compressed drug.
- Retaining of the drug at active site.
- clearance time is longer
- High therapeutic efficacy.
- High bioavailability.
- Dose proportionality.
- Faster dissolution of active agents
- Faster dissolution generally equates with greater bioavailability.
- Lesser drug doses.
- Less toxicity.

Disadvantages of polymeric nanoparticles

- Wide use of polyvinyl alcohol as a detergent –subjects with toxicity.
- Limited targeting capabilities.
- Termination of therapy is not possible.
- Cytotoxicity. (Naik *et al*., 2012)
- Pulmonary inflammation and pulmonary carcinogenicity.
- The trouble of autonomic inequity by nanoparticles consuming straight result on heart and vascular function.

Therapeutic Applications of Nanoparticles

- Carriers of drugs and biological agents
- Carriers of gene and DNA
- Carriers of antigens & vaccines
- Controlled and targeted drug delivery
- Carriers of diagnostic agent

Polymers Used for Preparation of Polymeric Nanoparticles

The picture is having four types of polymers are can be used for the polymeric nanoparticles formulations. The natural types of polymers are the obtained from the natural sources like animal or plants. The synthetic polymers are the prepared by the chemical synthesis methods. (Senthilnathan *et al*., 2015)

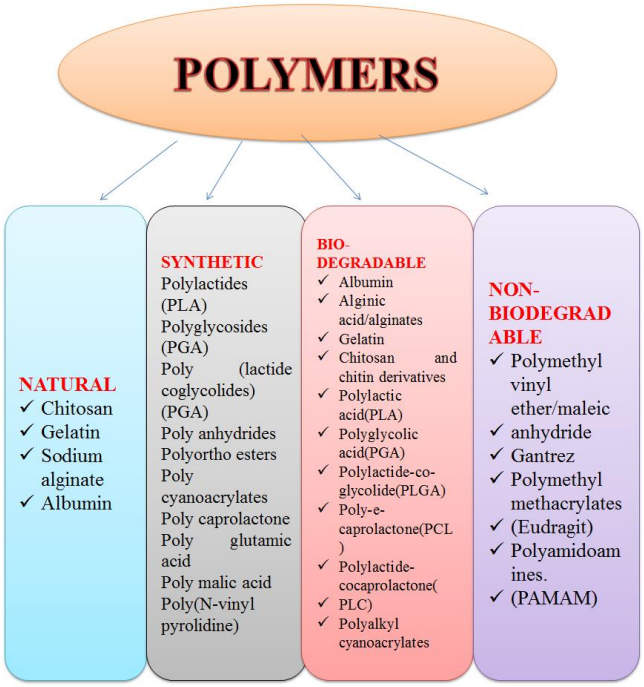

Figure 1: Types of polymers used for polymeric nanoparticles

PREPARATION METHODS FOR POLYMERIC NANOPARTICLES

The following preparation methods are the commonly used for the polymeric nanoparticles.

Emulsion-Solvent Evaporation Method:

This method involves two steps. The first step is emulsification of the polymer solution into an aqueous phase. In second step polymer solvent is evaporated, making polymer precipitation as nanospheres. The nano particles are collected by ultracentrifugation and washed with distilled water to remove additive deposit or any free drug and lyophilized for storage.[9]Modification of this method is high pressure emulsification-solvent evaporation method. This method involves preparation of an emulsion which is then subjected to homogenization under high pressure followed by complete stirring to eliminate organic solvent. The size of nanoparticles is controlled by regulating the stirring rate, type and amount of dispersing agent, viscosity of organic phase and aqueous phase and temperature.

Double Emulsion and Evaporation Method:

The disadvantage of emulsion-solvent evaporation method is poor entrapment of hydrophilic drugs. The double emulsion technique is overcomes this

disadvantage and encapsulate the hydrophilic drugs, which is done by the addition of aqueous drug solutions to organic polymer solution under vigorous stirring to form w/o emulsions. This w/o emulsion is added into second aqueous phase with continuous stirring to form the multiple emulsions (w/o/w emulsion). The emulsion then allowed to removal of solvent by evaporation, nanoparticles are isolated by centrifugation at high speed. The formed nanoparticles are carefully washed before lyophilisation.

Emulsions- Diffusion Method:

The polymer is dissolved in a moderately water-miscible solvent (for example propylene carbonate, benzyl alcohol), and saturated with water to ensure the initial thermo-dynamic equilibrium of both liquids. (Anusha *et al*., 2011) Then, the polymer-water saturated solvent phase is emulsified in aqueous solution having stabilizer, leading to solvent diffusion to the external phase and the development of nanoparticles, according to the oil-to-polymer ratio. Finally, the solvent is removed by evaporation or filtration, as said by its boiling point.

Salting Out Method:

In this method polymer and drug are primarily dissolved in a solvent which is afterward emulsified into an aqueous gel containing the salting out agent (electrolytes, for example magnesium chloride and calcium chloride, or non- electrolytes as sucrose) and a colloidal stabilizer for example polyvinylpyrrolidone or hydroxyethylcellulose. This o/w emulsion is dilute with an adequate amount of water or aqueous solution to increase the dispersion of solvent into the aqueous phase, hence the formation of nanoparticles.

Solvent Displacement / Precipitation method:

Solvent displacement includes the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in aqueous medium in the presence or absence of the surfactant. Polymers, drug, and lipophilic surfactants are dissolved in a semi-polar water miscible solvent for example acetone or ethanol. The solution is now poured or injected into an aqueous solution having stabilizer above magnetic stirring. Nano particles are formed immediately by the rapid solvent diffusion. The solvent is then removed from the suspensions under reduced pressure. This method is well suited for most of the poorly soluble drugs.

Dialysis

This method is created on a solvent displacement mechanism which includes extra tools for example dialysis tubes or semi-permeable membranes through suitable molecular weight cut-off which help by way of a physical barrier for the polymer. Therefore, dialysis is achieved against anon-solvent of the polymer miscible with the polymer solvent. The movement of the polymer solvent through the membrane induces a progressive loss of solubility of the polymer leading to the development of homogeneous nano suspensions.

Supercritical Fluid Technology

The supercritical fluid technology is globally harmless method for the making of polymeric nanoparticles. The usefulness of supercritical fluid has more ecological approach able solvents, and has the possible to produce polymeric nanoparticles with high purity and without any trace of organic solvent. This method is done by following two methods

- Rapid expansion of supercritical solution.
- Rapid expansion of supercritical solution into liquid solvent.

- Rapid Expansion of Supercritical Solution (RESS)

In this method, the solute is liquefied in a supercritical fluid to form solution, and then followed by the rapid development of the solution crossways the capillary nozzle into the ambient air. The rapid pressure reduction in the expansion results the homogeneous nucleation and the formation of fine dispersed particle.

- Rapid expansion of supercritical solution in to liquid solvent

This method is nearly like to the above method but in different to the RESS, the expansion of the supercritical solution in to a liquid solvent in its place of ambient air. The primary nano-sized particles are not allowed to produce in the expansion jet due to the occurrence of the liquid solvent. For example, polyheptadecafluorodecyl acrylate particles were produced using water as the solvent in which were expanded the supercritical solution and precipitated

the polymer. It was presented that the particle development results from the aggregation of originally formed nanoparticles.

Ionic gelation technique/coacervation of hydrophillic polymers

The decomposable hydrophilic polymers for example chitosan, gelatin and sodium alginate are used to formulate polymeric nanoparticles through ionic gelation method. This method contains combination of double aqueous phases, one is the polymer chitosan and the other is a poly anion sodium tri-polyposphate. The tool of this method is, positive charge amino group of chitosan interacts with the negative charge tripolyposphate to form coacervate with in its size range of nanometer. The coacervation of polymer and particles are made by the electrostatic interface among the two aqueous phases. In ionic gelation technique the material undergoing alteration from liquid to gel because of the ionic interaction state at room temperature.

DIABETES MELITUS

Diabetes mellitus has been known to manhood for over 2000 years. It is probable to become one of the most predominant and economically significant diseases of the 21stcentury in together the advanced and emerging nations. Diabetes Mellitus is a group of metabolic disorder considered by a whole lack of insulin, a comparative lack of insulin, or insulin resistance, which then results in hyperglycemia. (Deopa *et al*., 2013)

Diabetes mellitus is produced by changed metabolism of carbohydrate, lipid and lipoprotein subsequent from the fault in insulin secretion and action; it is characterized through symptom like hyperglycemia, glycosuria, polyphagia, polyurea, polydipsia, gradual loss of weight, fatigue, cramps, blurred vision, constipation, and candidiasis are prominent.(Harris *et al*., 1998) It is the most predominant chronic disease in the world affecting nearly 100 million people of the population where 5-10% having type 1 while 90-95% of them suffers from type 2 diabetes mellitus. Diabetes leads to many health complications such as hyperlipidemia, hypertension and atherosclerosis.

Classification of Diabetes

There are mainly four types of diabetes mellitus

- Type I diabetes or insulin dependent diabetes mellitus
- Type II diabetes or non-insulin dependent diabetes mellitus
- Gestational diabetes
- Genetically modified diabetes.

Type I diabetes can occur in any age. It is an immune mediated disease subsequent from destruction in β-cells of pancreas which leads to insufficient endogenous insulin making. Type II diabetes or non-insulin dependent diabetes mellitus is the most common type affecting old and obese individual produced either by insulin resistance or lacking insulin secretion. It is characterized by hyperglycemia in the presence of hyperinsulinemia due to peripheral insulin resistance. A third type of diabetes gestation diabetes mellitus is first recognize during pregnancy where hyperglycemic disorder develops in women who doesn't have diabetes result from an insufficient insulin supply to meet tissue demand for normal blood glucose regulation.(Fowler *et al*., 2008) Fourth type of diabetes is genetically modified diabetes mellitus there occur defects in β cell function or mutation of insulin receptor and may lead to diabetes. Other rare types of diabetes comprise persons caused by surgery, drug used (e.g. antihypertensive vasodilator diazoxide, lower dose of thiazides, corticosteroids in high doses, high dose of anabolic androgens, oral contraceptives, streptozotocin, theophylline, asprin, isoniazid, alloxan, nalidixic acid), malnutrition, infection and other illness.

Insulin and its secretion

The insulin is a polypeptide hormone its molecular weight of 6000 Da. It is initially produced as a single molecule (pre-proinsulin) contains 110 amino acids released by the pancreatic β-cells. These are regulates the glucose level in the system. It contains two polypeptide chains A and B. Chain A contains 21 amino acids and chain B having 30 amino acids. Two disulfide bonds covalently bind the chain where chain A contains an internal disulfide bridge. Hormone insulin is produced as pre- proinsulin in rough endoplasmic reticulum further by proteolysis it change to pro-insulin and then to insulin. After pre-proinsulin has passed through the endoplasmic reticulum, 24 amino acids are detached by enzymatic

action from one end of chain, leaving another form pro-insulin that undergoes folds and bonds to passes towards Golgi body where the central section of 33 amino acids is detached by the action of the enzymespro-hormone convertase1 and 2 converting to final structure of insulin. (Sanjukta *et al*., 2015)

Hypoglycemic Drugs

Anti-diabetic drug acts by two main mechanisms one is stimulation of β-cells in pancreatic islet to release insulin and another one is increase the sensitivity or amount of insulin receptor.(Fowler *et al*., 2008) Preoperatively, oral hypoglycemic agents, especially those that motivate insulin secretion, such as sulfonylurea and meglitinide agents, have possible for creating hypoglycemia during fasting prior to surgery. The sulfonylurea agents (e.g. glipizide, glyburide, glimepiride) are generally given oral hypoglycemic agents for the action of type 2 diabetes. These agents act by bind to the ATP-dependent potassium (KATP) channel in the pancreatic s-cells, leading to end of these channels and motivating insulin release. Thus, pancreatic β-cells are progressively responsive to glucose absorptions and insulin release is increased. Metformin, a biguanide oral hypoglycemic agent, is generally used for treatment of type II diabetes mellitus.α-glucosidase inhibitors are additional class of drugs that comprises compound like acarbose which delay the intraluminal production of glucose. Acarbose competitively stops α-glucosidase that is connected with the brush border membrane of the small intestine and responsible for the digestion of complex polysaccharides and sucrose. Natural compounds may be another management as they can be comprised in everyday food and can be taken in larger amount without any risk. Many plants are identified in traditional medicine of different culture to be used for their anti-diabetic property.

Polymeric Nanoparticles for diabetic treatment

The polymeric nanoparticles are the advanced method of the treatment of diabetes mellitus which having the several advantages and the novel drug delivery system. The using of the polymeric nanoparticles is the effective treatment of diabetes mellitus. The table.1 is having the various polymeric anti-diabetic drugs, polymers used for the formulation and the formulation methods.

Table 1: Polymeric Nanoparticles for diabetic treatment

s. no	Drug used	Polymer used	Method of preparation	Reference
1	Metformin	Ethylcellulose (EC), Poly (lactic-co-glycolic acid) (PLGA), Poly (methyl methacrylate) (PMMA), and Chitosan	solvent evaporation method	Dhanalekshmi Unnikrishnan *et al*., 2015
2	GLIPIZIDE	Polycaprolactone	Emulsification-solvent evaporation technique	Jitendra Naik., *et al.* 2013
3	Glipizide	Eudragit RL100	solvent evaporation	Priyanka Saharan *et al.,* 2015
4	Pioglitazone Hydrochloride	Chitosan	Solvent Displacement Method	A. Umar faruksha *et al.,* 2013.
5	Glipizide	PLGA and Eudragit RS 100	Single emulsion solvent evaporation method	Pratap Naha *et al.,* 2012.
6	Glibenclamide	Poly (lactic-co-glycolic) acid	emulsification solvent evaporation method.	A Behera *et al.,* 2012.
7	Insulin	Chitosan	Ionotropic gelation method	Mounica Reddy M *et al.,* 2012
8	Human insulin (Mw ~ 5800 Da)	PLGA	double emulsion method	Yasemin Budama-Kilinc *et al.,* 2017
9	Human insulin 100	polycaprolactonetriol	precipitation polymerization	Pijush Kumar Paul

	IU/mL)		method	*et al.,* 2017
10	Porcine insulin (30 IU/mg)	Chitosan	polyelectrolyte ionotropic gelation	ZhiyangK *et al.,* 2015
11	Costusspeciosus leaves	polylactic-co-glycolic acid (PLGA)	solvent displacement technique	Wagdy K. B. Khalil *et al.,* 2014

CONCLUSION

The polymeric nanoparticles are formulated by drug with the polymers. The main advantages of the polymeric nanoparticles are the simplest preparation method, targeted delivery, the minimizing of the dose and high therapeutic efficiency. In this review was concluded that the polymeric nanoparticles are the advanced method of the treatment of diabetes mellitus.

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