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Review

Recent advances in nanotechnology for the treatment of metabolic syndrome

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ABSTRACT

Metabolic syndrome is a main clinical challenge of global health which is growing universally. It would be resulted from over-consumption of energy, increased obesity, and lack of movement during life. The metabolic syndrome causes a five-fold increase in the risk of type 2 diabetes mellitus and a double increase in the risk of rising cardiovascular disease over the next 5–10 years. Based on this, more attention has been drawn to the diagnosis and treatment options of this disease. Nanotechnology is one of the preferred methods for improving this disease. This way is a natural development in many health domains, including synthetic and nanostructures. The use of nanoparticles with the purpose of increase the effectiveness of treatment, decrease the side effects and the amount of drug usage, through their small size, permeability and maintenance strength lead to their absorption by target organs. Meanwhile, different nanoparticles with consumption values and particle size have been investigated.

1. Introduction

The history of the metabolic syndrome began in 1920 when a Swedish physician showed the association between hypertension, high blood glucose (hyperglycemia), and gout [1]. Later in 1947, it was explained that abdominal obesity is commonly associated with the metabolic syndrome observed in cardiovascular disease and type 2 diabetes [2]. Based on this, in 1965, an abstract in the EU was presented at an annual meeting for a study on diabetes that described the syndrome again, which consist on blood pressure, blood glucose and obesity [3]. It is considered as the first risk factor for the onset of complications of arterial thrombosis. In fact, metabolic syndrome is defined by a combination of metabolic, clinical, biochemical and physiological factors that directly increase the risk of cardiovascular disease, atherosclerosis, type 2 diabetes, and cause death [4,5]. Interestingly, it is caused by complex interactions between genetic factors and the environment such as insulin resistance, abdominal obesity, atherogenic dyslipidemia, endothelial dysfunction, genetic sensitivity, hypertension, over coagulation and chronic stress [5].

Metabolic syndrome included the insulin resistance, central obesity, dyslipidemia, and hypertension which are the risk factors for cardiovascular disease among adults [6–8]. Panel III (NCEP ATP III) has been widely advised in the recognition and treatment of people with metabolic syndrome before cardiovascular disease [9]. Although the exact prevalence of the metabolic syndrome is unknown, some evidence suggests that its occurrence is alarmingly progressing [9]. A study in Tehran has shown that the popularity of this syndrome among adolescents is more than 30% [10], which is higher than developed countries such as the United States [11]. Therefore, it seems that genetic, metabolic and environmental factors such as diet have an important role in its development [12]. The metabolic syndrome as defined by ATP III, is characterized by three or more of the following factors as presented in Table 1:

According to Table 1, the all criteria for the presence of metabolic

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Table 1
ATP III clinical identification of the Metabolic Syndrome.

Factor	Level	
	Men	women
Fasting plasma glucose		≥6.1 mmol/L
TG		≥1.7 mmol/L
Abdominal obesity waist circumference	>102 cm	>88 cm
SBP		≥130 mmHg
DBP		≥85 mmHg
HDL-c	<1.03 mmol/L	<1.3 mmol/L

syndrome are the circumference of the abdomen which is equal to or greater than 102 cm in men and 88 cm in women, blood pressure equal to or above 130/85 mmHg, fasting blood glucose level of 110 or more and triglyceride Equivalent to above 150 mg/dL, HDL cholesterol levels below 40 and less than 50 mg/dL in men and women, respectively. The metabolic syndrome in patients are associated with a 2–4 fold increased risk of stroke, 3 to 4 times increased risk of myocardial infarction, and 2-fold increase in mortality in compare with non-syndrome patients [13] without the background of cardiovascular disease [14].

The spread of syndrome depends on the area, urban or rural environment and structure (gender, age, race, and ethnicity) of the population studied [15,16]. High economic status, low mobility, lifestyle and high body mass index are significantly linked with metabolic syndrome. Preventive methods for developing a metabolic syndrome include lifestyle changes, initial weight loss, and exercise. Treatment includes the appropriate use of pharmaceutical agents to reduce certain risk factors. Drug therapy should be used for people who have not reduced their risk factors through preventive and lifestyle modifications [17]. Nanotechnology is a new phenomenon to treat some diseases. There is the lack of epidemiological studies about the health effects of nanomaterial publicity. Nevertheless, according to our knowledge about the features of nanoparticles in foods, there is a potential possibility of non-differential exposure in epidemiological studies, which tends to drive relative risk estimations to zero [18]. Recent evidences showed that exposure to nanoparticles were associated with oxidative stress and inflammation-related DNA damage in liver and lung [19,20]. Metabolic syndrome elevated the risk of cardiovascular diseases [18]. According to some experimental studies, nanoparticles exposure caused endothelial dysfunction in rats with metabolic syndrome. So we can conclude that nanoparticles affect metabolic syndrome.

2. Triglycerides and HDL blood

Recently, the use of nanoparticles and their harmful or beneficial effects have attracted more attentions from the biomedical scientists. The effect of nanoparticles on the level of serum triglyceride was investigated. Increasing of triglyceride levels may be does not show any relevant symptoms but it can slowly cause to the large disturbances such as cardiovascular events. Typically, it is recommended that serum triglycerides should be maintained below 150 mg/dL [21].

In this regard, a research by Role et al.(2013) about the effects of silver nanoparticles on the activity of lactate dehydrogenase and cardiovascular changes in male Wistar rats was done. It was resulted that the short-term use of these nanoparticles was unable to change the dehydrogenase enzyme levels [22]. Also, Rezaei et al. (2011) investigated the toxicity of different doses of silver nanoparticles on lung tissues of male rats. The changes in some biochemical and hematological parameters in the blood Wistar rats were co-administered with long-term oral administration of silver nanoparticles. The results indicated that there was no significant change in blood cholesterol levels, but the level of triglyceride decreased significantly after three months [23].

Similar to the previous results in the nonbinding study, oral nano silver particles had a moderating effect on blood triglyceride. Regarding to this matter, Ismaili et al. investigated the effect of silver nanoparticles on clinoptilolite on liver enzymes and lipid concentration in broiler chicks. They observed that the concentration of enzyme alanine aminotransferase and alkaline phosphatase decreased significantly. Concentrations of cholesterol, triglyceride, LDL, and VLDL decreased, while, HDL concentration increased. They emphasized that silver nanoparticles coated with clinoptilolite could improve their health [24]. However, in the study of Mousavi and colleagues, blood triglyceride was not affected by manganese oxide nanoparticles [25]. More accurate studies are needed to identify the mechanism and the effect of the reduction of silver nanoparticles on blood triglyceride levels. Table 2 provides a summary of studies to improve the efficacy of drugs used in lipid profiles using nanoparticles (see Table 3).

3. Diabetes and blood glucose

The most common symptoms of a person's metabolic syndrome include high blood pressure, high blood glucose, and triglycerides. In normal conditions, the concentration of blood glucose in a narrow range is typically controlled between 80 and 90 mg/dl in the morning before breakfast in the fasting person. This concentration rises to 12–140 mg/dl at about 1 h after a meal. But feedback systems for controlling blood glucose return normal glucose concentrations, a bit higher for diabetics. Increasing blood glucose levels can damage many tissues, especially blood vessels, which may result in heart attacks, stroke, and kidney disease [9,26]. In a study using 30 ppm nanoparticles of silver, no effect on the level of glucose was observed. Since the liver enzymes have not changed, this condition implies the safety of these compounds. However, conflicting results are expected. Mousavi et al. [25] showed that injection of 100 μg/kg nanomangan (85-85 nm) into rats in two weeks once and for 14 weeks increased glucose and reduced HDL. Although manganese are critical to maintaining the function and proper adjustment of many biological processes, high doses can be toxic. According to mentioned study [25], prolonged exposure to manganese nanoparticles negatively affects blood biochemical factors, especially blood glucose in animals. They also observed significant weight gain. In justification of the observed results, the manganese nanoparticles have high oxidation power. Manganese was proposed as mitochondria-rich organs (especially the liver, pancreas and pituitary) is transferred to accumulate [27]. The ability of nanoparticles of magnesium in the body production of oxygen reactivation and stimulate lipid peroxidation, causing an imbalance in the level of liver enzymes and antioxidant responsible for cellular damage, which may cause scar tissue or glucose observed in tested [25]. Hu and colleagues studied the effects of oral administration of nanoparticles of titanium dioxide to zero, 64 and 320 mg per kg of body weight per day for 7 days, the mice were examined and the results showed the plasma glucose increased [28]. Studies have shown that silver nanoparticles have a significant reduction in blood glucose levels, higher serum insulin levels, increased glucokinase activity, higher expression of insulin, insulin receptor, glucokinase and GLUT-2 genes in diabetic rats. They showed that silver nanoparticles and zinc oxide could act as potential anti-diabetes agents. In addition, researches have also sought to use nanoparticles for treating diabetes.

A). Type 1 diabetes: Due to the destruction of insulin secreting cells in the pancreas.

Table 2
Work done of different nanoparticles with hyperlipidemia.

Drug	formulation	Size	Inference	Reference
Atrovastatin calcium	Chitisan nanoparticles	150.5 ± 1.24 nm	Effective carrier for controlled drug delivery	Bathool et al., 2012
Chitisan	Chitisan nanoparticles	500&1000 nm	Non-toxic and useful in lowering body weight and serum lipid	Zhang et al., 2011
Lovastatin	Nanostructured lipid carrier	180–290 nm	More stable in gastric environment and improve the clinical efficacy of lovastatin	Chen et al., 2010
Protein	Protein- nanoparticles conjugates	100 nm	Digestion of bad cholesterol	Maximor et al., 2010
Estradiol	Oral estradiol nanoparticles	100 nm	Reduced dose and frequency	Mittal et al., 2009

Table 3
Overview of previous studies on the effects of nanoparticles on various factors in metabolic syndrome.

Reference	Type and amount of nanoparticles	Results
Wang et al. (2007)	Titanium oxide nanoparticles	Undesirable toxic effects on the cell and pulmonary fibrosis and tumors in animal models
Role et al. (1392)	Silver nanoparticles	Do not change the amount of enzyme dehydrogenase in short-term use and as a result of the safety of consumption.
Ismaili et al. (1395)	Silver nanoparticles deposited on clinoptilolite on liver enzymes and blood lipid concentration in broiler chicks	The concentration of enzymes of alanine aminotransferase and alkaline phosphatase decreased significantly. Concentrations of cholesterol, triglyceride, LDL, and VLDL decreased and HDL concentration increased
Rezaei et al. (2011)	Silver nanoparticles	Uncontrolled blood cholesterol levels, significant reduction in blood triglyceride levels in rats after three months.
Alkaladi et al. (2014)	Silver nanoparticles and zinc oxide at daily doses of 10 mg/kg	Decrease blood glucose
Gheibi et al. (1395)	Silver nanoparticles(30 ppm)	Adjustment effect on triglyceride, no effect on blood glucose level
Mousavi et al. (2016)	Manganese Nanoparticles (100 μg/kg) (25–85 nm)	Increased glucose and reduced HDL, no effect of blood glucose suppression, significant weight gain.
Kobyliak et al. (2017)	Nano Crystal Cerium Dioxide (nCeO2)	Reducing the level of pro-inflammatory cytokines (IL-1β, IL-12Bp40) and anti-inflammatory cytokines (IL-4, IL-10, TGF-β) in the control group in the rat serum.
CHen et al. (2013)	Gold nanoparticles (μg AuNPs/g 85/7) on male rats	The decrease in fat mass significantly, the accumulation of gold nanoparticles in the abdominal fat and to a degree in the liver Obscure toxicity for vital organs. A solution to treat obesity and obesity related to diseases.
Xu et al. (2016)	Rosiglitacin coating and derivative of prostaglandin, using outer shell of nanoparticles including PEG polymer	Transformation of white fat tissue into brown tissue and increased angiogenesis and fat loss.
Antal et al. (2015)	Magnesium nanoparticles of aliskiren using mannitol (Fe3O4) as magnetic and polyhedrons, lactate as a polymer	Reduced systolic blood pressure.
Kim et al. (1997)	Three polymer nanoparticles comprising Poly-epsilon-caprolactone poly-epsilon-caprolactone (PCL), poly lactic and glycolic acid (1: 1) and Eudragit RL/RS Eudragit	Reduce blood pressure
Yu et al.(2016)	Poly (lactic-coglycol) acid nanoparticles (PLGANP)	Reduce blood pressure
Hirst et al. (2013)	Cerium nano oxide is given to mice for 2 or 5 weeks at 0.5 mg/kg	The results are similar to a common treatment for oxidative stress reduction

B). Type 2 diabetes: Due to progressive insulin secretion, insulin resistance is caused.
C) Gestational diabetes: Diabetics diagnosed during pregnancy.

Symptoms include overweight, increased urinary excretion, excessive thirst, excessive desire to eat (overeating), etc. [29] Nanotechnology has already had a significant impact on the diagnosis and treatment of diabetes The use of nanoparticles has been done with the aim of delivering insulin.

4. Types of nanoparticles for delivery of insulin

4.1. Polymer nanoparticles

Nano-cells and nanocapsules which included coarse molecular objects of size 10–1000 nm [30]. These nanoparticles have very different characteristics and follow a matrix system [31,32]. Nanocapsules are vesicular systems that block the drug in a cavity surrounded by a single polymer membrane. These compounds are decomposed into biocompatible components by hydrolysis, and thus, the drug is encapsulated into the target tissue. The analysis process also takes place in the volume section, where the matrix is parsed equally or at the polymer level, which is the free-flowing rate associated with the surface space. The polymer is decomposed into lactic acid and glycolic acid, which is eventually converted to water and carbon dioxide via a crumb wheel. Past research focused on the use of natural polymers such as collagen, cellulose as biodegradable systems [33]. In a new study, an insulin delivery system based on nano particles consisting of dextran sulfate and chitosan in aqueous solution was investigated. These nanoparticles exhibited efficacy at about 85%. Insulin release at a pH less than 2.5–24 h was almost not observed, however, in a controlled form at pH equal to 6.8 insulin [34]. Today, attention is focused on chemically synthesized polymers, such as polyester, polyurethanes and polyethylene ethacrylates. Recent polymer nuggets have been synthesized on the basis of polyethoxy (ethylene glycol) and di-blocked di-lactic polymeric copolymers [35]. Dextroin nanoparticles-vitamin B12 are another example of these nanoparticles that prevent the destruction of insulin by digestive enzymes, in particular intestinal proteases [36].

4.2. Dendrimers

Dronerimers are new, three-dimensional polymer systems with the dimensions ranging from 10 to 20 nm, with improved physical and chemical structure. These compositions have the same size,

weight and uniformity. Their internal cavity can be well filled with water-repellent drugs and water-wells. The dendrimers are made up of an atomic atom such as nitrogen, which carbon and other the components are added by chemical reactions through repetitive sets and creates a spherical branching structure. Ultimately, its size is similar to that of albumin and hemoglobin [37] (see Fig. 1).

4.3. Ceramic nanoparticles

Ceramic nanoparticles consist of calcium phosphate, silica, aluminum or titanium. Ceramic nanoparticles have certain advantages, such as ease of preparation, biocompatibility, very small size (less than 50 nm) and good volumetric stability [38]. These particles effectively protect the molecules against the anti-denaturation due to the changes in pH and external temperature. These particles can be produced in size, shape and porosity. The nucleus of calcium phosphate nanoparticles is used as an insulin carrier. The disadvantages of these compounds are its poor permeability from the mucous membrane and the rapid disappearance of the mucosylation mechanism of the nano-constituent formulation of the nasal congestion injected intravascularly [39].

4.4. Micelles

Myslla consists of surfactant molecules or amphiphilic macromolecules and its structure has an oceanic core and a water-like surface that can act as a solubility factor. Their size is less than 100 nm [40,41].

4.5. Liposomes

A combination of lipid molecules is obtained in aqueous solution. Their structure has the water-soluble groups toward the center and the water-loving groups are oriented toward the outside of the molecule, thus forming a double layer spherical membrane. On this basis, it is possible to download water-loving drugs in the nucleus, and water-borne drugs in the liposome shell [42]. Their advantages are non-toxicity, lack of immune response, biodegradability, stability, particle size distribution, and the ability to enclose it [39]. Studies have shown that using coatings such as chitosan coatings and polyethylene glycols increasetheir physical stability (83). The most widely used phospholipid in the liposome structure is phosphatidylcholine with a hydrophilic polar head called phosphocolin, a glycerol bridge and a hydrocarbon chain acid [43].

Fig. 2 shows the liposomal bearing nano that a drug in the liposome is embedded by the encapsulation process. These carriers increase the solubility of drugs and improve their pharmacological properties, such as chemotherapy, fast metabolism, reduction of harmful side effects, and increased antinociceptive activity both in and out of the body [44].

4.6. Newosomes

Because of the sensitivity of liposomes to the rapid heating and oxidation of the main constituent of their own structure, the use of more stable and biocompatible compounds as alternatives to phospholipids was introduced. These types of vesicles were considered for cheap, high stability, ease of maintenance of raw materials and final formulation, as well as access to wall complex surfactants. Newzoms are used to deliver the following: Drug medications with peptide and protein compounds such as alpha interferon, bovine serum albumin, influenza virus antigens, GnRH-based contraceptive immunogens, insulin, cyclosporine A, and the like. This drug delivery method improves the absorption of drugs and improves its effectiveness or reduces its side effects [45].

4.7. Biomechanics system for delivery of medication

Microelectromechanical systems are a technology for the reduction and it is widely used in the field of medical engineering. Although the most commonly used system for making sensors during surgery (for example, intragastric pressure measurements), long-range sensors for prosthetic devices and advanced sensors for laboratory diagnosis, they can be used as insulin pumps for controlled release InsulinOne of the suggested models for this work is a medicinal tank section that can be filled with insulin molecules. In this system, biosensors and porous nano membranes are placed in pores with a diameter of 6 nm in the outer portion to detect changes in blood glucose levels and release insulin into the reservoir. In this system, nano biocapsules with microfiber membranes with a pore size of 18 nm are used to deliver insulin [39].

4.8. Nanopumps

These pumps can pump insulin in a constant proportion to the patient's body and balance the blood sugar. These nano-pumps can also be used for drugs with low levels of use over a long period of time [46].

4.9. Chitosan-combined golden nanoparticles

These compounds are also good carriers for insulin and lowering

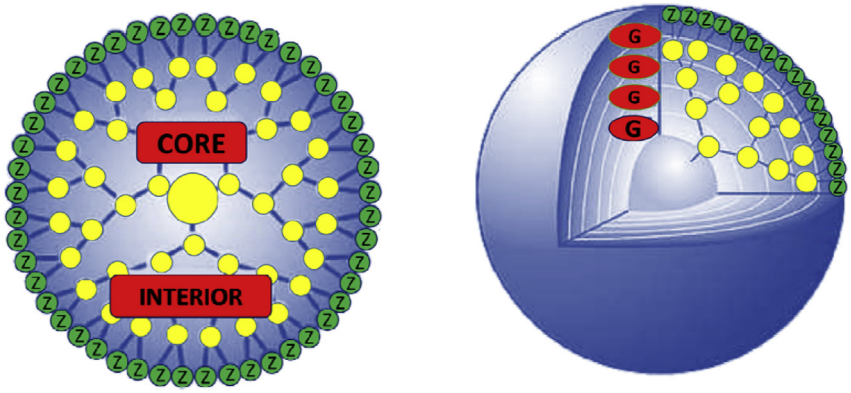

Fig. 1. A spatial shape of a dendrimer including a nucleus that contains molecular information such as size, shape, orientation, and number, the interior that is the area of amplification of the cellar branches and the surface (active end groups) of the polymerization region of the pattern.

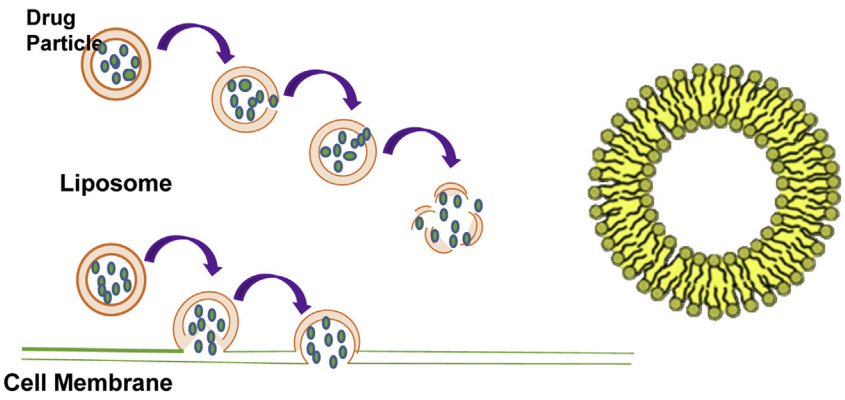

Fig. 2. The structure of liposomes, which are internal to outward, consisting of aqueous nucleus, two-layer phospholipid membrane and stabilizing polymer, and delivery of medication by them.

blood glucose levels. Also they cause a loading of 53% and a relative insulin resistance. The use of chitosan doubles the blood glucose lowering effect. Improving penetration and facilitating the passage of insulin through oral and nasal mucus, long-term stability, proper insulin loading, and increased pharmacodynamic activity of insulin are the benefits of using this compound. Its disadvantages are its high distribution in organs such as the liver, spleen, kidney, brain, heart, stomach and joints [39]. Researchers are trying to access nanoscale drugs and systems for delivering insulin, particularly oral or inhalable, using nano-carriers. This new generation of effective diabetes treatment can be useful in improving the quality of the diabetics life who are forced to inject daily insulin. Correcting these nanocarriers may lead to successful nano-formulation of oral or respiratory insulin in future clinical sets [47].

5. Abdominal obesity and fat tissue

The global epidemic of obesity is increasing day by day as it is considered as the fifth risk factor for death [48]. The mortality rate for obese individuals is at least 20% higher than those with normal weight [49]. Obesity has many correlations with related diseases, such as cardiovascular disease, type 2 diabetes, all types of cancers (except esophageal cancer in women), asthma, bladder diseases, inflammation of the joints and chronic lower back pain [49]. In obese people, fat metabolism is impaired, resulting in fat accumulation in the body. In a trial, using single dose of gold nanoparticles (85.87 μg/g) on male rats, 72 h after injection, daily energy intake and body weight were similar to that of the control group. Although the fat mass was significantly smaller than the controled group. After injection, gold nanoparticles accumulated in the abdominal fat and somewhat accumulated in the liver. At the end, it was suggested that the nano-nature of gold can be used as a strategy for the treatment of obesity and obesity-related diseases [50]. It has been suggested that particles with a diameter of 1–2 nm are usually toxic, whereas gold nanoparticles with a diameter of more than 15 nm are usually inexpensive, unlike the tested non-toxic cell type [51]. Net gold nuggets of 17 and 37 nm cause anorexia, weight loss, changes in skin color, and liver damage [52]. On the other hand, obesity due to monosodium glutamate was observed and fatty tissue under the influence of nanoparticles was reduced and decreased. In this study, cerium oxide nanoparticles were used at a size of 2–5 nm. The precise mechanism of this phenomenon remains unclear, but it is suggested that it is somewhat related to the strong antioxidant activity of the study compound [53]. According to the previous results, weekly injections of serum nano oxide for 0.5–2.5 mg/kg for 2 or 5 weeks in mice with CCl4-induced liver toxicity were similar to those seen with N-acetylsitin-treated mice, a commonly used treatment for reducing oxidative stress is indicated [54].

Researchers have recently devised a new method for treating obesity. In this method, by injecting anti-obesity drugs into high-fat tissues by doping plant nanoparticles, the fat tissues can be burned with the least side effects of waste fats. In order to burn fat, it is first necessary to turn white fat tissue from fat-storage cells into brown tissues. Anti-obesity drugs increase the growth of new blood vessels in the adipose tissue, in addition to allowing an easier conversion of the white tissue to brown tissue, strengthening the nanoparticle targeting process. According to researchers, the advantages of this method is that by targeting a particular area, we do not see the systemic effects of the reaction elsewhere in the body. In previous studies, experiments performed on laboratory mice showed that the increase in the growth of new blood vessels (angiogenesis) help to reduce the weight of the mice, but medications used in the vein can lead to damage to other parts of the body. To overcome this problem, the drug delivery method was selected with nanoparticles. The researchers designed particles that carry the drug in their hydrophobic nucleus. This method, which is required for a known polymer called PLGA, is used in many other dosing agents. This polymer consists of end-to-end connections between poly (lactic-coglycolic acid) -b-poly (ethylene glycol) and an endothelial target peptide. They inserted two different types of drugs into nanoparticles: Rosiglitazone, which is approved for the treatment of diabetes, but is not used due to side effects, and another derivative of prostaglandin, which is a type of human hormone. Both drugs stimulate PPAR cell receptor, which stimulates the angiogenesis and transformation of adipose tissue. The outer shell of the nanoparticles includes a PEG polymer, embedded with the molecule that directs the particles towards the target. Eventually, these molecules bind to proteins in the blood vessels that surround the adipose tissue. The researchers tested these particles in the body of a rat that became obese after a fatty diet. It was observed that in addition to a 10% reduction in mouse weight and a 30% lower level of cholesterol, a significant reduction in triglyceride levels and a three-fold increase in serum insulin production was observed. The problem with this is that penetration of the intestinal wall is difficult for nanoparticles. In the new study, a new oral method has been used. In this method, a protein that is responsible for the transport of iron in the human body is used to facilitate the carriage of nanoparticles throughout the intestine. Researchers hope by inventing new methods, they will be able to find the target adipose tissue, and also to reduce the possible side effects of less toxic drugs [55].

6. Blood pressure

Rising blood pressure becoming a major global burden, which is an important risk factor for cardiovascular disorders, such as myocardial infarction, stroke, cardiac failure and peripheral vascular disease [56]. The challenges facing antihypertensive drugs include bioavailability, dose and side effects, which greatly affects their efficacy. Various studies have argued that nano-carriers can significantly increase the bioavailability of drugs by reducing the number of doses, as well as minimizing the toxicity of using high levels of drugs. Nanoparticles have been reported to increase the absorption of drugs through various mechanisms, which include intracellular uptake, paracellular transfer by opening the solid binding site, inhibiting P-gp, inhibiting the intestinal wall metabolism by CYP450, and increasing lymphatic transport [57]. In a study of aliskiren magnetic nanoparticles using magnetite as magnetic and polydehyde compounds, L-lactide was prepared as a polymer. Reduced systolic blood pressure to 153.8 ± 3.9 mmHg compared to placebo and aliskiren suspension with systolic blood pressure of 203.4 ± 4.3 and 178.7 ± 1.8 mm Hg, respectively. The success of the study was blood pressure treatment [58]. Similarly, the Val-Leu-Pro-Val-Pro model was developed for the antihypertensive peptides based on nano-particle delivery system based on poly (lactic-coaglyolate) nano-particles, and its antihypertensive effects on mice blood pressure was checked. VP5 nanoparticles had a particle size of 2323.7 ± 2.23 nanomaterial and an encapsulation efficiency of $87.37 \pm 0.92\%$. Laboratory results indicated a long-term (96 h) free-radical release with antihypertensive effects and increased efficacy in vitro. This study showed that PLGANP is a suitable formula for the delivery of oral medications for small peptides of hypertension [59]. The use of Nifedipine, a medicine used to treat hypertension, is limited due to the very rapid onset of activity and short biological half-life. In order to eliminate these disadvantages, nanoparticles were prepared from three different polymers of poly-epsilon-caprolactone, poly-lactic acid and glycolic acid (1: 1) and Oedrajit. The diameter of the nanoparticles ranged from 0.29 to 0.21 μm, and the capsule ratio was 82%–88%. This test was performed on mice with hypertension and it was observed that blood pressure decreased significantly, the median survival rate and bioavailability were increased, and the drug was released and sustained. In the treatment of pulmonary hypertension, drugs such as pitawactatin, NF-KB decoy, imanitib, braaprost, using the PLGA drug delivery systems, and fosodil and anti-RNA-145 antibodies were used in the liposome system to reduce drug complications and improve efficacy (92).

With regard to recent advances, various methods have been developed for the use of nanoparticles as shown in Fig. 3.

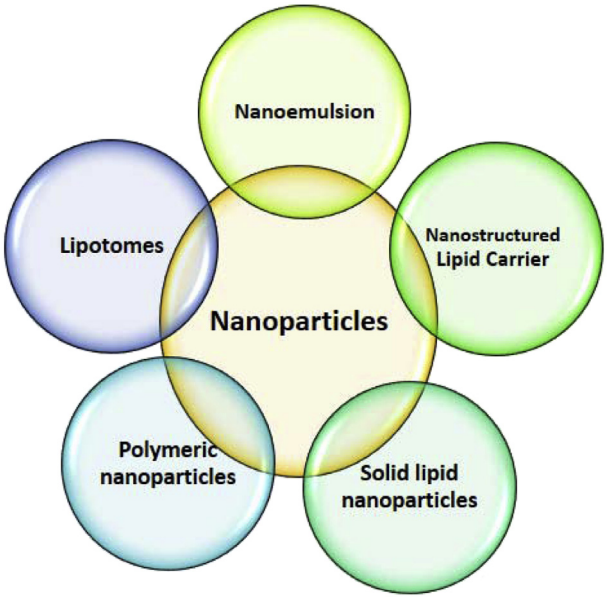

Fig. 3. Different forms of nanoparticles used to treat high blood pressure.

6.1. Nanoparticles

Polymeric nanoparticles based on a polymer that is widely used for oral medications for high blood pressure lactide-co-glycolide include polystyrene, poly-caprolactone, Eudragit, hydroxypropyl methyl cellulose and chitosan. The drugs released from these nanoparticles are influenced by the method of preparation, particle size, surface active agents, polymer molecular weight, and polymer structure [56]. The pH-sensitive polymers can deliver to targeted drugs in the special areas of the digestive tract. While drugs that are susceptible to degradation in the lower gastrointestinal tract, such as Oderrajit L100-55, can be used at a controlled rate to deliver the drug [56].

6.2. Chitosan nanoparticles

Chitosan is naturally degradable, biocompatible and is non-toxic to the human body.

6.3. Fat Buminant nanoparticles

Many antihypertensive drugs are provided using a fat delivery system. Fat-based nanoparticles are good choices for the delivery of antihypertensive drugs that have low solubility and high permeability. Fat-based diluents can leach more fatty friendly drugs than hydrophilic drugs.

6.4. Liquid emulsion

Emulsion liquid contains a self-emulsifying drug delivery systems for micro, self-emulsifying drug delivery systems, nanotechnology, microemulsion and nanoemulsion [56].

6.5. Nano-emulsions

Nono-emulsion is a thermodynamically stable delivery system that can dissolve a high amount of medication. It is a fast operating agent with a high maintenance timeand can provide a high oral bioavailability [60].

Solid Fat Nanoparticles: Solid Fat Nanoparticles are composed of diluents (drug adsorbents) that are biocompatible and include solid fats and surfactants/co-surfactants. The fat diluents used are monoglycerides, di-glycerides and triglycerides of fatty acids with different chain lengths. The highly complex fats are a combination of these fatty acids with very incomplete crystals to inject more of the drug into it. The liberation of the drug from fat nanoparticles is two phase, with constant release after initial release. Single release can be minimized by reducing the build-up temperature and concentration of surfactant. Fat nanoparticles increase the bioavailability of the drug by preventing the first pathway of lymphatic absorption [47].

6.6. Fat carriers with a nanoscale structure

Fat nanoparticles have some limitations, such as drug withdrawal due to the formation of solid fats to very complete crystals over time, resulting in reduced loading capacity and harvesting

efficiency over time [56].

6.7. Lipotomes

This type has two fat-based new functionalities of nano-carriers that have been developed for lysedipine, a weak soluble drug. Lipotomes are prepared using a liquid ethanolic alcohol and surfactant of the Tween 80 by a thin membrane hydration method [61].

6.8. Inflammation

Inflammation is the result of a series of well-regulated events. It involves the expanding cascade as a result of a stimulus and it is an important process that compensates the body for damaging to the tissue and protects itself against foreign substances. Acute inflammation is typically due to the chemical, mechanical, or pathogenic effects, which have a relatively short duration (several hours to several days). Chronic inflammation does not require any external stimulus and can create a range of painful and debilitating symptoms. Theuncontrolled inflammations often indicate very serious underlying causes, which can be a diagnostic marker for some conditions, such as autoimmune diseases, infections, neurology, cardiovascular disease and metastasis [62]. In a study, anti-inflammatory properties of nano-crystalline cerium dioxide were investigated on inflammation and it was shown that the content of pre-inflammatory cytokines in rats were decreased and anti-inflammatory cytokines were increased to control group levels [53]. The fifth generation of nanoparticles of polydendrimer (amidouamine) conjugated covalently into folic acid polylanthate as a target ligand for macrophages as well as the activity of a conjugated dendrimer, FA-methotrexate as a treatment for inflammation of arthritis was studied. Folate was transplanted with dendriram and in a specific way the receptor was inserted into the macrophage cell binding of the beta-receptor of folate and early macrophages of the mouse. The results showed that G5-FA-MTX acted as a potential anti-inflammatory agent and reduced arthritic inflammatory parameters such as knee swelling, leg volume, cartilage damage, bone resorption and body weight [63]. Nano-carrier systems are useful in response to stimuli such as pH, temperature, or oxidation-reduction potential during inflammation to overcome some intracellular and systemic delivery dams [64]. Anionic liposomes containing phosphatidyl ethanolamine are formulated for delivery of analgesic oligonucleotides. At low pH, it is possible to mix endosomal membranes and destabilize endosomes that are useful in the treatment of viral infections, cancer, or inflammatory diseases [65]. Endomethacin was co-administered with copolymer nuclides from Poloxamer and Polyepsilon-Caprolactone. They were able to reduce damage, unlike size and temperature, compared to endomethacin alone [65]. In another study, gold nanoparticles were used to provide pluronuclear mucosal shells, which showed a temperature-sensitive swelling/temperament behavior. This feature of the micelles in increasing temperature was due to the hydrophobic interaction of the plochasmic copolymer chain linked to the micelles structure [66]. Magnesium nanoparticles loaded with endomethacin have been identified as an appropriate anti-inflammatory drug among magnetic drugs. However, the poor solubility of these compounds in water with their successful encapsulation in the poly-lactic acid magnetic nanoparticles was eliminated by nano-deposition method. This combination showed a very good response to external stimuli [67].

Nano-carriers of anti-inflammatory drugs are susceptible to oxidizing agents and concentrations; physiochemical changes (such as swelling or water-solubility) facilitate very rapid release of released molecules (such as anti-inflammatory drugs). In the end, these carriers should be removed (for example, through renal excretion) in order to eliminate the possible side effects of their long-term presence in the host's body. At the end of their life whspan, carriers should be converted to water-soluble compounds with a low molecular weight [67].

7. Conclusion

The prevalence of metabolic syndrome due to the urbanization, inactivity and excessive consumption of energy is increasing, and since this disease is the source of many other diseases including diabetes, atherosclerosis, heart attacks and so forth, seeking therapies for this is vital. By Summarising the above findings, it can be concluded that nanotechnology plays a very important role in improving the efficacy of many medications. These compounds increase the function of drugs by keeping them from breaking down or providing constant release. Therefore, they can be beneficial in reducing the amount of drug used or its side effects in the treatment of many diseases, such as metabolic syndrome. The methods and compounds used are very diverse, and here we refer to the related issues of metabolic syndrome. Other compounds with different properties, such as nano-fibers and silicone compounds, are also used to treat other diseases and carry different drugs [68]. However, there are many challenges in the direction of nanoformation, such as particle size, cost of production, repeatability, stability and regulation, which remains unclear. Since overcoming the low bioavailability of oral medications is done using the opportunities and limitations of nanoparticle formulation, further studies are needed in this regard.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.03.002.

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