World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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Floating microspheres: Emerging delivery system for diabetes mellitus

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World Journal of Biology Pharmacy and Health Sciences, 2022, 11(03), 026–035

Publication history: Received on 07 August 2022; revised on 14 September 2022; accepted on 16 September 2022

Article DOI: https://doi.org/10.30574/wjbphs.2022.11.3.0121

Abstract

In order to increase bioavailability, stability, and target the drug to a specific region at a predetermined rate, floating microspheres, multi-unit drug delivery systems, are designed to accomplish controlled or delayed drug administration. In clinical practise, drugs that have an upper small intestine absorption window may benefit the most from a controlled drug delivery system with an extended stomach residence period. The non-uniformity of medication absorption throughout the gastrointestinal tract and the heterogeneity of gastrointestinal (GI) transit time across and among subjects are the two key issues. The most common drug delivery systems in these applications are floating or hydrodynamically controlled. Gastro retentive medication delivery is a method of extending the length of gastric residency because it targets site-specific drug release for local or systemic effects in the upper gastrointestinal tract (GIT). Due to the uniform distribution of these multiple-unit dose forms in the stomach, which encourages more repeatable medicine absorption and a lower risk of local discomfort, floating microspheres are becoming more and more popular. Compared to single-unit dosing variants, these systems offer more benefits. The physiology of stomach emptying is briefly examined in the context of floating drug delivery systems in this paper. This review's objective is to compile the most recent research on preparation techniques and other factors that affect the functionality and characterization of floating microspheres.

Keywords: Diabetes; Floating Microspheres; Gastroretentive; Insulin; Glucose

1. Introduction

1.1. Diabetes

Diabetes is a chronic metabolic condition that affects how proteins, lipids, and carbohydrates are metabolised. A weak or insufficient insulin secretor response, which causes impaired carbohydrate utilisation, is a defining feature of diabetes mellitus and the subsequent hyperglycemias (glucose) [1]. the most typical endocrine illness is diabetes (DM), a condition also known as "sugar." Normal signs and symptoms include a deficiency or absence of insulin or, less frequently, an abnormal insulin response (insulin resistance) [2]. The International Diabetes Federation (IDF) predicts that by 2025, there will be 69.9 million diabetics in India, up from the current 40.9 million [3]. The islets of Langerhan's include both beta (ß) and alpha (4), which release insulin and glucagon, respectively. By encouraging glycogenogenesis and delivering glucose to the muscles, liver, and adipose tissue, insulin lowers blood sugar levels. The latter are erythrocytes and brain tissue, whereas alpha (5) cells play a crucial role in controlling blood glucose by secreting glucagon, which increases blood glucose levels by accelerating glycogenolysis, and glucagon. In the fetus's postnatal life, there is an increased risk of obesity, metabolic, cardiovascular, and cancer disorders [6]. Type II diabetes accounts for 80–90% of all cases of diabetes mellitus. The severity of the issues and total morbidity and mortality can vary depending on the location [7, 8]. Location can influence how serious the problems are and how many people get sick or die [7, 8]. Modest exercisers also have a very slight reduction in their risk of dying compared to those who aren't active. There is

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currently a lot of evidence to support the idea that such an occurrence requires a specific genetic composition [9]. The increased incidence of diabetes and other non-communicable diseases is one of the primary health challenges to the WHO African Region's nations' ability to thrive economically [10].

1.1.1. Classification of Diabetes

The World Health Organization (WHO) released the first classification of diabetes mellitus between 1980 [11] and 1985 [12]. This session will focus on primary or idiopathic diabetes, the most common and serious kind of diabetes mellitus. It must be distinguished from secondary diabetes mellitus, which involves hyperglycemia with known causes, including surgery, tumours, certain medicines, iron overload (hemochromatosis), and specific acquired or inherited endocrinopathies, which lead to the loss of pancreatic islets [13].

Insulin Dependent Diabetes Mellitus (Type1 IDDM)

It was previously known as juvenile onset diabetes. Diabetes is currently referred to as a "autoimmune disease." The patient may require treatment for various autoimmune disorders in addition to Graves' disease, Hashimoto's thyroiditis, and Addison's disease [14]. Type 1 diabetes, is a serious, potentially fatal condition that typically develops swiftly [4]. Children and young adults are most frequently affected. Patients with type 1 diabetes and the autoimmune processes that lead to beta-cell loss commonly have antibodies against anti-insulin, anti-islet cell, and anti-glutamic acid decarboxylase, among others [2]. Senescent b-cells, which are the primary cause of type 1 diabetes and frequently lead to an utter lack of insulin (American Diabetes Association, 2014). There are numerous ways in which beta cell apoptosis can happen, with some people experiencing it fast and others more gradually [15]. The destruction of the pancreatic ß-islets results in a substantial decrease or absence of insulin production. Insulin injections are required for treatment [3]. 85–90% of persons with Type 1 diabetes display immune destruction markers, such as autoantibodies to insulin, glutamic acid decarboxylase (GAD), in their blood when fasting diabetic hyperglycemia is first detected [16].

Non-Insulin Dependent Diabetes Mellitus (Type2 Niddm)

Type 2 diabetes is a different name for adult-onset diabetes. In the context of insulin resistance, the progressive insulin secretor malfunctions [17] (American Diabetes Association, 2014). When a person has this type of diabetes, insulin frequently acts in a resistant manner [18]. They are the primary causes of morbidity and mortality from diabetes [1] and have an adverse effect on blood vessels, kidneys, eyes, and nerves in both cases. The causes are complex, and heredity, sedentary behaviour, middle-aged and older age, and obesity are among the predisposing variables. The risk of macrovascular and microvascular problems is therefore higher in these patients [19, 20].

Gestational Diabetes Mellitus

This disorder is known as gestational diabetes mellitus (GDM), which is used to refer to glucose intolerance that is discovered or manifests itself for the first time during pregnancy [21]. Gestational diabetes mellitus, or GDM, is a term used to represent both Type 1 and Type 2 diabetes mellitus that develops in pregnant women or is detected during pregnancy but is undiagnosed and asymptomatic [13]. Gestational diabetes mellitus (GDM) is a kind of diabetes that is not fully under control throughout pregnancy [14]. Type 2 diabetes and obesity are more likely to occur in children born to women who had gestational diabetes mellitus. The results of prenatal exposure to hyperglycemia are thought to be the source of this condition.

Other Specific Type (Monogenic Types)

Mutations in the hepatic transcription factor hepatocyte nuclear factor (HNF)-1a, which is found on chromosome 12, are the primary cause of the most prevalent form of monogenic diabetes. They also went by the name beta cell genetic deficiencies. These types of diabetes typically have early-onset hyperglycemia as a distinguishing feature (generally before age of 25 years). They are also referred to as those who have exocrine pancreas illnesses like pancreatitis or cystic fibrosis, people whose endocrinopathies (such acromegaly) are connected with pancreatic dysfunction, and people whose pancreas is damaged by drugs, chemicals, or infections [13]. In addition, several medicines are used in conjunction with HIV/AIDS treatment or following organ transplants. A tiny number of families experience proinsulin conversion disorders caused by genetic faults that inhibit the production of insulin. These disorders are inherited via an autosomal dominant inheritance pattern. They are only in charge of less than 10% of DM cases [11].

1.1.2. Treatment of Diabetes Mellitus

In addition to giving patients a lot of insulin every day, the treatment's objective is to get rid of the trigger. Insulin usage returns to normal after the condition is under control. One way to achieve the goals of managing diabetes mellitus is to:

- To preserve comfort and safety while restoring the diabetic's aberrant metabolism to normal as closely as feasible.
- To slow or stop the progression of the disease's hazards over the short- and long-term.
- Give the patient the information, inspiration, and tools necessary to perform this self-advanced care.

1.1.3. Therapies Involved In Diabetes Mellitus

Stem cell therapy

Monocytes and macrophages may play a substantial role in the emergence of these persistent inflammatory states as well as insulin resistance in T2DM patients, according to research [22]. A cutting-edge technique called stem cell educator therapy can be used to prevent or treat immunological dysfunctions [23]. Closed-loop blood collection from the patient is followed by the separation of lymphocytes from the remaining blood, co-cultivation of the lymphocytes with adherent cord blood-derived multipotent stem cells (CB-SCs), and injection of the educated lymphocytes back into the patient's circulation [23].

Antioxidant therapy

Patients with type 2 diabetes have been treated for oxidative stress using a variety of antioxidants, including vitamins, dietary supplements, and active ingredients derived from plants, and medications. To combat oxidative stress and its side effects, vitamin C, vitamin E, and beta-carotene are the best supplements [24]. Antioxidants, which have been shown to significantly reduce the chance of acquiring diabetes and its complications.

Dietary Management

Enough caloric value Patients with diabetes and those without the disease should practise proper dietary control, such as:

- Balanced in terms of protein, carbohydrates, and fats; under all circumstances, carbohydrate consumption must be limited.
- Should adhere to norms as nearly as possible
- Meals should be spaced out regularly and be of a comparable size.
- Cut back on both fat and carbohydrate intake to lower total calorie intake.
- The patient needs to be advised to maintain his daily eating habits.

Newer Insulin Delivery Devices

Many advances have been achieved to make administering insulin easier and more accurate while also achieving tight glycemic control. These include insulin pens, insulin pumps, implanted pumps, inhaled insulin, insulin pumps, and various insulin administration methods.

Oral Hypoglycaemic or Antidiabetic Agents

Clinically useful biguanide phenformin was created in 1957, concurrent with the sulfonylureas' development. As a result of the ongoing research into innovative methods, thiazolidinediones, meglitinide analogues, -glucosidase inhibitors, and most recently, dipeptidyl peptidase-4(DPP-4) inhibitors have recently been created [25].

1.1.4. Epidemiology

Diabetes was predicted to affect 552 million people globally by 2030, up from the estimated 366 million cases in 2011. [26] With 80 percent of those affected living in low- and middle-income countries, type 2 diabetes is on the increase globally. In 2011, 4.6 million individuals died from diabetes. The anticipated number of people who will have type 2 diabetes by 2030 is 439 million. [1,26] The occurrence of type 2 diabetes varies greatly by location as a result of environmental and behavioural risk factors. A review of the literature revealed that there are little figures on the prevalence of type 2 diabetes across all of Africa [27, 28]. Studies examining data patterns show that there has been a marked increase in prevalence that equally affects both sexes over the whole continent of Africa [29]. Less than 10% of instances of diabetes are brought on by type 1 diabetes; type 2 diabetes seems to be the main cause of diabetes in Africa [29]. In 2010, there were 25.8 million diabetics in the US (7.9% of the population), and 90 to 95% of those cases were type 2 diabetes, according to a 2011 estimate from the Centers for Disease Control and Prevention . [30] It is anticipated that type 2 diabetes, which is already more common than ever before, will become more common among individuals

who already have the disease during the next 20 years. In emerging nations, where this development will be most pronounced, patients are primarily between the ages of 45 and 64 [31]. Because of the continuous transition from infectious to non-communicable diseases, the latter is predicted to eventually equal or perhaps surpass the former in emerging nations, resulting in a double burden [32].

Diabetes mellitus (DM) is now the fifth most prevalent cause of mortality in the majority of developed and developing nations, having become a global epidemic over the past few decades. According to the International Diabetes Federation's (IDF) most recent atlas, which estimates that there are currently 382 million individuals with diabetes worldwide [33]. That figure is anticipated to increase to 592 million by 2035.

Diabetes mellitus is a chronic hyperglycemic metabolic illness with several etiologies characterised by abnormal protein, lipid, and carbohydrate metabolism. The two primary types of DM are Type 1 and Type 2. Type 1 DM is mostly brought on by complete insulin insufficiency; however, Type 2 DM can also be brought on by various degrees of insulin resistance, reduced insulin secretion, and increased glucose production. Other Type 1 DM subtypes include type 1B idiopathic insulin deficiency (IDI) and type 1A Type 1 DM, which is characterised by the autoimmune destruction of cells. All types of DM were anticipated to be controlled ever since 1921, when insulin emerged as a feasible therapy option. However, Type 2 DM was well controlled after taking oral hypoglycemics. Other approaches, with various degrees of effectiveness, include pancreas transplantation and gastric bypass surgery. It is recommended to alter one's lifestyle to manage gestational diabetes mellitus (GDM) both during and after pregnancy. This includes strict dietary control, regular exercise, routine checkups by analysing blood sugar levels, and special care is needed after the baby is delivered as the mother may be more likely to develop T2DM [34].

1.2. Floating microsphere

Gastro-retentive drug delivery systems are also known as floating microspheres. Technically speaking, hollow microspheres are spherical, empty, free-flowing powders made of proteins or synthetic polymers, with diameters purposely ranging from 1 to 1000 microns. Floating microspheres are systems that are buoyant enough to float over the contents of the stomach for a considerable amount of time. To lessen the risk of unanticipated swings in plasma drug concentration, the medication is administered gradually at the suggested rate. By reducing the frequency of administration and enhancing patient compliance, floating microspheres can enhance the therapeutic effects of medications with short half-lives. Medicines that only dissolve in the stomach, a higher rate of medication absorption, and longer intervals between gastric emptying [35].

The bulk density of hydro-dynamically balanced systems (HDBS) or floating drug delivery systems (FDDS) is lower than that of gastric fluids, allowing them to float in the stomach for extended periods of time without having an impact on how quickly the stomach empties.

1.2.1. Advantages of FDDS [36, 37]

Some of these advantages include the following:

- Better dosage form occupancy at the absorption site and improved GRT lead to better medication absorption.
- Safe administration of drugs.
- Drug administration to the stomach for localised effect.

1.2.2. Disadvantages of FDDS

- A number of variables, including stomach motility, pH, and the presence of food, might affect gastric retention. Since these variables are never consistent, it is impossible to forecast buoyancy.
- Drugs should not be developed as floating drug delivery systems if they irritate or damage the stomach mucosa.
- The gastric emptying time varies greatly depending on whether the process is complete or not.

1.2.3. Types of FDDS

The development of FDDS based on the mechanism of buoyancy has utilised non-effervescent and effervescent systems, two distinctly different technologies:

Non-Effervescent FDDS

The matrix-forming polymers polyacrylate, polycarbonate, polystyrene, and poly-methacrylate, as well as hydrocolloids of the cellulose type, polysaccharides, and polysaccharides, are frequently used in the production of the FDDS that fall into this category. [38] As the medication in the dose form diffuses in and out of the gel structure, the diffusing solvent forms a "receding boundary" within the gel structure. [39] These systems can appear in a variety of forms:

- Single Layer Floating Tablets
- Bi-layer Floating Tablets
- Alginate Beads
- Hollow Microspheres

2. Effervescent FDDS

The buoyant delivery method used either matrices with chambers of liquid that gasify at body temperature or matrices made of swellable polymers like Methocel or polysaccharides (like chitosan) with effervescent substances like sodium bicarbonate, citric acid, or tartaric acid 40, 41]. These effervescent systems fall into two more types.

- Gas Generating systems
- Volatile Liquid/Vacuum Containing Systems.

2.1. Methods of Preparation of Floating Microspheres

2.1.1. Spray Drying

The polymer needs to be dissolved in an adequate volatile organic solvent before it can be spray dried. Drugs are quickly homogenised into the polymer solution while they are still in solid form. The dispersion is then atomized with the aid of a hot air stream. The atomization process creates small droplets or fine mists, which are then converted into microspheres with sizes ranging from 1 to 100 m. These microspheres have a quick solvent evaporation [42].

2.1.2. Solvent Evaporation

Solvent evaporation procedure is completed during the liquid production vehicle phase. The liquid manufacturing vehicle phase is immiscible with the volatile solvent in which the microcapsule coating is distributed. The coating polymer solution contains a dispersion or dissolution of a core substance to be microencapsulated. The core material combination is disseminated in the liquid production vehicle phase with agitation in order to create the correct size microcapsule [43].

2.1.3. Ionic gelation method

In this procedure, the cross-linking agent, polymer, and copolymer were mixed with purified water to create a homogeneous mixture of polymers. The medication and polymer dispersion were completely mixed with a magnetic stirrer to produce a homogeneous dispersion. Calcium chloride was dissolved in glacial acetic acid at a 2 percent concentration to create the gelation medium. A homogeneous alginate solution was extruded into the gelation media using a syringe needle. After being collected, the microsphere underwent two cleanings in distilled water before being allowed to dry for 24 hours at room temperature [44].

2.1.4. Single emulsion technique

The natural polymers are first distributed in an aqueous medium, such as water, and then in a non-aqueous medium, such as oil. The dispersed globule is subsequently put through the cross-linking process. The cross-linking can be produced using both heat and chemical crosslinkers.

2.1.5. Double emulsion technique

Water-soluble drugs, peptides, proteins, and vaccines are the best candidates for the double emulsion approach, which calls for the creation of multiple emulsions or the double emulsion type w/o/w. The protein present in the scattered aqueous phase is typically finally encapsulated in the polymer solution of the continuous phase. The original emulsion is homogenised before being converted into a double emulsion.

2.1.6. Phase separation coacervation technique

The steps in this process involve spreading a polymer solution containing drug particles, adding an incompatible polymer to make the first polymer phase separate, and then allowing the second polymer to swallow the drug particles. Non-solvent application causes a polymer to start hardening right away. As soon as the process of generating microspheres begins, agglomerates must be avoided since the polymerized globules produced start to adhere together and do so. The solution must be forcefully stirred at the proper speed for this.

2.1.7. Spray drying and spray congealing

These techniques rely on airborne medicinal mist and polymer drying. Depending on whether the solvent is withdrawn or the solution is cold, the two separate processes of spray drying and congealing behave differently. The heated air is removed from the microparticles using a cyclone separator, and any remaining solvent is vacuum dried off to create porous microparticles [44, 45].

2.1.8. Quasi-emulsion solvent diffusion

Micro sponges can be created from an external phase containing polyvinyl alcohol and distilled water by employing a quasi-emulsion solvent diffusion technique. Medicine, polymer, and alcohol make up the inner phase. The outer phase and internal phase must first be combined at ambient temperature before creating the interior phase at 60°C. Immediately upon emulsification, the mixture is continually agitated for two hours. Once the micro sponges are gone, the mixture can be filtered.

2.2. Strategies for Gastric Retention

There are numerous ways to increase a dose form's gastric retention time (GRT) in the stomach [46].

2.2.1. Systems for Floating Drug Delivery

Low-density systems with hydrodynamic regulation, commonly referred to as floating systems, float or remain buoyant in the stomach for a considerable amount of time without changing the rate at which the stomach empties. They have a lower bulk density compared to stomach fluids [46]. The medicine floats on the contents of the stomach, gradually and continuously leaving the body. When a drug is ejected from the stomach, the residual system is emptied, which enhances the body's capacity to regulate variations in plasma drug concentrations and raises GRT [47]. Systems with a floating chamber filled with air, vacuum, or inert gas can float in the stomach [48].

2.2.2. Systems with Bio/Muco-adhesive

Bio/muco-adhesive systems have the ability to lengthen the gastric residency time of drug delivery systems in the stomach by improving the closeness and duration of the drug's interaction with the biological membrane.[49] The adhesion of polymers to the mucin/epithelial surface can be classified according to three main criteria:

- Adhesion mediated by hydration
- Adherence caused by bonding.
- Adhesion that is receptor-mediated

2.2.3. Expanding and Swelling Systems

These are the dosage forms that, after being consumed, swell to an extent that prevents them from passing through the pylorus. The dosage form subsequently undergoes a prolonged transit time through the stomach. These systems are known as "plug type systems" because they frequently continue to be stopped at the pyloric sphincter when their enlarged diameter exceeds 12 to 18 mm. When in touch with stomach fluid, the polymer expands and absorbs water. These polymeric matrices could stay in the stomach for a few hours even after eating.

2.2.4. Voluminous systems

These systems are situated in the rugae of the stomach, which can endure peristaltic movements and have a density of around 3 g/cm3. Such systems can only fit in the lowest parts of the stomach when their density is between 2.6 and 2.8 g/cm3. The usage of coated pellets is common in high-density formulations. Iron powder, barium sulphate, zinc oxide, and titanium dioxide are just a few examples of the heavy inert elements used in coating production [50].

2.2.5. Including Food Agents That Delay Passage

This method involves feeding the stomach digestible polymers or food excipients such salts of myristic acid to alter its pattern into a fed state, which slows down gastric emptying and facilitates a significantly longer release. Saturated fatty acids with a chain length of C10–C14 are the most common culprits for the delayed stomach emptying that follows fatty meals. [50]

2.2.6. Resins for ion exchange

Ion exchange resins packed with bicarbonate are added to medications that have a negative charge. To prevent the carbon dioxide from exiting the beads quickly, a semi-permeable barrier is then added. A chloride and bicarbonate ion exchange takes place once food reaches the stomach's acidic environment. This process results in the release of carbon dioxide, which then becomes caught in the membrane. Resin-coated beads rise to the top and form a layer that floats, in contrast to uncoated beads, which sink instantly in the stomach [51].

2.2.7. Systems with osmotic regulation

It is made comprised of a bioerodible capsule, an inflatable floating support, and an osmotic pressure-controlled medication delivery system. The osmotically regulated intragastric medication release device quickly releases the medication from the capsule. A flexible, hollow polymeric bag that is inflated is created inside the inflatable support from a liquid that, when heated to body temperature, gasifies. The device is made up of the drug reservoir section and the osmotically active compartment. [52]

2.2.8. Applications of floating microspheres [53]

- Antiviral, antifungal, and antibiotic medications, which can only enter the body through very specific sections of the GI mucosa, can be transported by floating microspheres.
- Hollow microspheres are particularly effective at minimising the main side effect of stomach discomfort and enabling controlled release of non-steroidal anti-inflammatory drugs. Floating indomethacin microspheres can be particularly beneficial for those with rheumatic diseases.
- Delivering insoluble and hardly soluble drugs using floating microspheres yields the best results. It is well known that the time available for medication dissolution reduces as a drug's solubility increases, making transit time a crucial component in drug absorption. By limiting the delivery of these medications to the stomach, hollow microspheres may reduce the probability that their poor solubility at an alkaline pH may wind up being the rate-limiting step. Drugs like verapamil hydrochloride, which is effectively absorbed by the stomach, benefit from positioned gastric release. By favourably changing the active agent's absorption profile, the gastro retentive floating microspheres will increase the substance's bioavailability

3. Conclusion

Floating controlled drug delivery systems are employed to solve this problem of low bioavailability of drug and poor absorption of drug at target site. Drug absorption in the gastrointestinal tract is a fickle process and prolonged gastric retention of the dosage form extends the time for drug absorption. Floating microspheres is highly acceptable gastroretention strategies of drug delivery that provides an efficient means of enhancing bioavailability and controlling the release of many drugs.

Compliance with ethical standards

Acknowledgments

The authors express gratitude to School of Pharmaceutical Sciences, SGRRU, and Dehradun.

Funding source

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of conflict of interest

The authors declare that there is no conflict of interest that could be prescribed as prejudging the impartiality of the review. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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