

MICROBALLOONS: A NOVEL APPROACH TO MITIGATE DIABETES**Shubham K. Chaudhari*, Pankaj M. Pimpalshende, Satish B. Kosalge****Hi-Tech college of Pharmacy, Padoli, Chandrapur (M.H)***Corresponding Author's E mail: shubham.choudhari58@gmail.com

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ABSTRACT

Diabetes is a long-term metabolic disease marked by the body's incapacity to control blood sugar levels. The prevalence of diabetes has increased significantly due to dietary and lifestyle choices. Novel therapeutic approaches have been investigated to control diabetes and mitigate the dangers related to current medication. Advanced microspheres have been created by certain researchers recently, either for the delivery of insulin and anti-diabetic medications or for diagnostic use. The creation of controlled or sustained delivery products with a quick start of action and enhanced bioavailability is made possible by these microspheres. The purpose of this study is to present an overview of diabetes, contemporary treatments, innovative drug delivery methods specifically, microballoons and previously developed microballoons for anti-diabetic medications. There is much promise for incorporating novel approaches in the diagnosis and treatment of diabetes with microballoons. There may still be issues with these approaches' scalability and practical applications that need to be resolved.

Keywords: Diabetes, NDDS, Microballoons, Antidiabetic drugs.

INTRODUCTION

Diabetes mellitus is a chronic illness that has been linked to a three- to four-fold increase in cardiovascular morbidity and mortality. It also has one of the greatest societal and healthcare expenditures. In actuality, the primary cause of death for individuals with diabetes is ischemic heart disease. On the world health agenda, type 2 diabetes mellitus (T2DM) is strongly regarded as a global pandemic that poses a threat to both human health and global economies. Over the past 20 years, the number of people with type 2 diabetes has more than doubled globally ¹. The International Diabetes Federation estimates that 415 million people worldwide have type 2 diabetes in 2015; by 2040, that figure will have increased to over 642 million. Based on these estimations, the global prevalence in 2015 was 8.8% (95% confidence interval: 7.2–11.4%), and the global prevalence in 2040 is expected to be 10.4%

(95% confidence interval: 8.5–13.5%). Disease prevention should be given top emphasis since epidemiological data indicate an unstoppable and unsustainable increase in global health spending linked to type 2 diabetes ^{2,3}.

The pathophysiology of diabetes must be understood in order to treat it. As a result, there is a substantial insulin secretion deficit in type 1 diabetes mellitus, for which insulin or an insulin analog is now the sole treatment available. On the other hand, type 2 diabetes mellitus is a somewhat more complicated condition in which early on insulin resistance is predominant. Insulin resistance continues in more advanced levels, but the deficiency in insulin secretion is more noticeable ⁴.

Preventing or delaying the onset of late disease complications, preventing acute decompensation, lowering mortality, and maintaining a high quality of life are the key objectives of diabetes management. Regarding long-term health issues, it is evident that maintaining appropriate blood sugar levels can lower the risk of microvascular problems (such as neuropathy, nephropathy, and retinopathy). However, maintaining appropriate blood sugar levels alone may not be as important in preventing macrovascular problems (such as peripheral artery disease, ischemic heart disease, and cerebrovascular disease) ⁵. Thus, treating hyperglycemia should be considered an integrated element of treating the three risk factors (smoking, dyslipidemia, and arterial hypertension [AHT]) that these individuals have. Therefore, it makes little sense to pursue perfect glycemic control at the expense of other cardiovascular risk factors. Even if targets are not strictly met for any of the cardiovascular risk variables, treating them altogether will undoubtedly benefit the diabetic patient more in the long run ^{6,7}.

List of Antidiabetic Agents

Alpha-Glucoside Inhibitors

Acarbose, Miglitol Biguanides Metformin, Phenformin Glitazones (Thiazolidinediones) Rosiglitazone, Pioglitazone, Troglitazone

Insulin and Insulin Analogue Sulfonylureas

First-Generation Sulfonylurea: Tolazamide, Tolbutamide, Acetohexamide, and Chlorpropamide.

Second-Generation Sulfonylurea

Glyburide, Glipizide, And Glimepride Glinides (Meglitinides) Repaglinide, nateglinide, mitiglinide ⁸.

Even though a plethora of drugs are hitting the market, a full and effective treatment for diabetes mellitus has yet to materialize because of the numerous side effects they might bring, including nausea, injection anxiety, stomach discomfort, and more. As a result, these drugs eventually cause noncompliance from the patient and necessitate highly skilled medical knowledge. It might be more advantageous to find

reliable, non-invasive drug delivery combined with regulated release. While precise and safe delivery of drugs to specific sites for predetermined periods of time to achieve controlled and sustained release is still a benchmark, pharmaceutical researchers have primarily worked to alter the biological and physical barriers that prevent drugs from reaching therapeutic targets⁹⁻¹⁰.

In recent times, novel drug delivery systems, or NDDSs, have gained popularity because to their apparent advantages: less dose intervals, higher bioavailability, protection against degradation in the hostile stomach environment, site specificity, and fewer side effects. Numerous studies conducted globally in vitro, ex vivo, and in vivo have firmly indicated that NDDSs are a new and potential treatment option for important illnesses and diseases¹¹.

Microballons: A novel drug delivery system for treating diabetes

A number of strategies, including single- and multiple-unit systems, have been developed to extend the stomach residence duration of dosage forms. These strategies include hydrodynamically balanced systems and floating drug delivery systems. Although single-unit floating systems are more widely used, they have a drawback in that the large variability of the gastrointestinal transit time is caused by their "all-or-nothing" emptying procedure¹². However, because the multiple-unit dosage forms are supposed to lessen dose dumping probability and inter-subject variability in absorption, they might be a preferable option. With the ability to disperse broadly throughout the gastrointestinal tract (GIT), this dosage form offers the chance for a more consistent and prolonged release of the medication from the dose container¹³. Pharmaceuticals with site-specific absorption from the upper gastrointestinal tract that have low bioavailability could be designed as floating drug delivery systems to maximize absorption¹. Oral bioavailability is increased and overall gastrointestinal transit time is prolonged when drug delivery devices are retained in the stomach.

Microballoons

In a strict sense, microballoons are spherical, hollow particles devoid of a core. The microballoons are made of synthetic polymers or proteins and are characterized by their free-flowing powder, with a maximum size of 200µm. The use of solid biodegradable microballoons with a medicine dissolved or distributed throughout the particle matrix offers the possibility of a regulated drug release. Low density systems that have enough buoyancy to float over gastric contents and stay in the stomach for an extended amount of time are known as gastro-retentive floating microballoons. The medication is gradually given at the appropriate pace as the device hovers over the stomach contents, increasing gastric retention and minimizing variations in plasma drug concentration. Simple solvent evaporation or solvent diffusion / evaporation methods were used to prepare microballoons loaded with drugs in their other polymer shell

in order to extend the gastric retention time (GRT) of the dosage form by continuously floating over the surface of an acidic dissolution media containing surfactant for >12 ¹⁴⁻¹⁵.

Advantages of microballons

- Reduces the dosing frequency and thereby improve the patient compliance. • Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects and despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
- The use of hollow microballoons increases gastric retention duration due to buoyancy and reduces material density.
- Better absorption of medications that only dissolve in the stomach
- Long-term, controlled drug release
- Medication delivery to the stomach that is site-specific is possible. Superior to single unit floating dosage forms as such microballoons releases drug uniformly and there is no risk of dose dumping.
- The continuous release action helps prevent gastrointestinal discomfort
- Short half-life medications can have better therapeutic effects. (Dhole *et al.*, 2011; Somwanshi *et al.*, 2011).

Mechanism of Drug Release

When stomach fluid comes into contact with microballoons, the gel formers, polysaccharides, and polymers hydrate to produce a colloidal gel barrier that regulates the rate at which fluid enters the device and, as a result, the release of medication. The hydration of the neighboring hydrocolloid layer preserves the gel layer when the dosage form's outer surface dissolves. The air that the expanded polymer traps reduces density and gives the microspheres buoyancy. However, in order to achieve buoyancy properly, a minimum stomach content is required. Microballoons of acrylic resins, Eudragits, polyethylene oxide, and cellulose acetate; polystyrene floatable shells. Polycarbonate floating balloons and gelucire floating grains are the current advances.

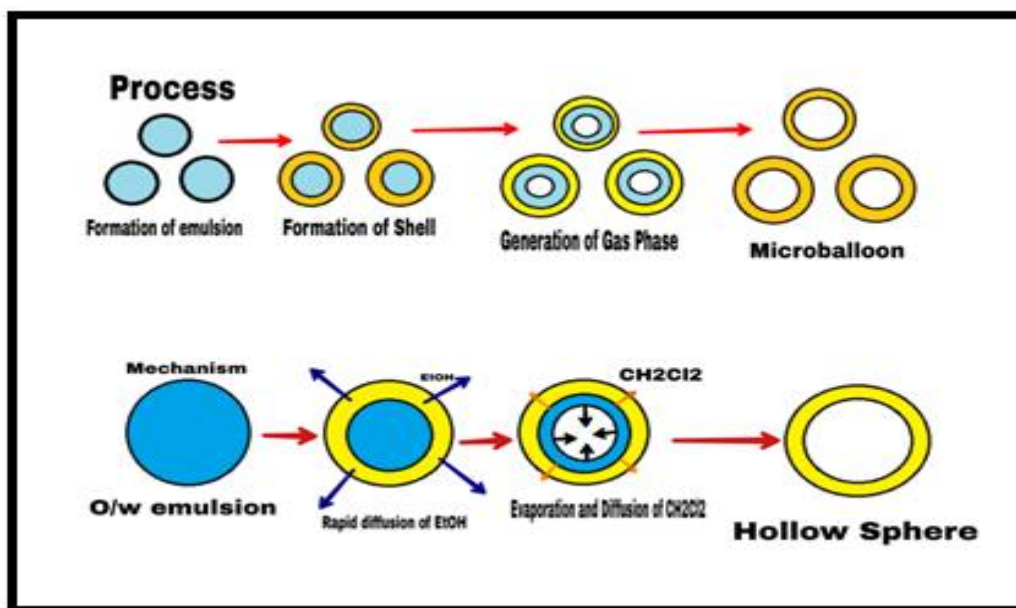


Figure 1: Pictorial representation of microballons

Methods of preparation of microballons

Emulsion Solvent Diffusion Method

This approach involves adding a polymer and drug solution in ethanol, methylene chloride, to an agitated poly vinyl alcohol aqueous solution. The ethanol quickly separates into the external aqueous phase, and the polymer precipitates around the methylene chloride droplets. The entrapped methylene chloride evaporates, causing internal cavities to form inside the microparticles^{18,19}.

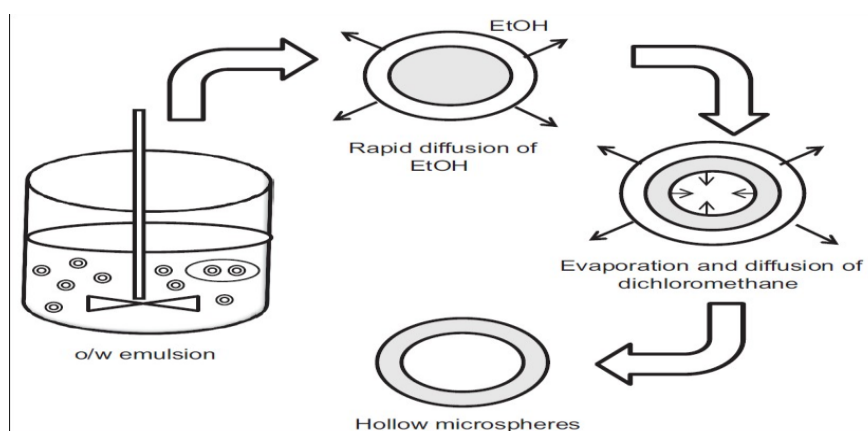


Figure 2: Process of Emulsion Solvent Diffusion Method

Spray drying

A molten coating material can be thermally congealed to complete the coating solidification process. Solvent removal can be achieved through sorption, extraction, or evaporation.²⁰

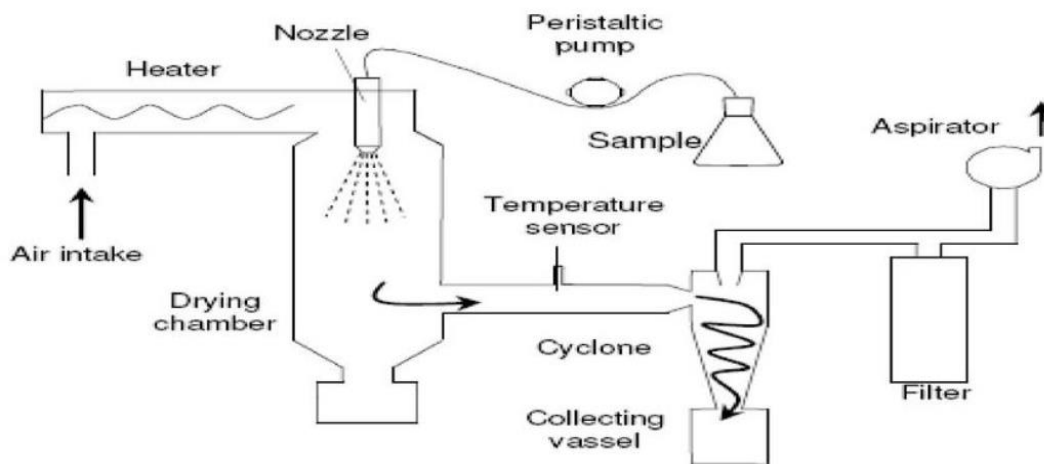


Figure 3: Preparation of microballons by spray drying

Solvent diffusion evaporation technique

This technique somewhat modifies both the emulsion solvent diffusion technique and the emulsion solvent diffusion technique. The medication is combined with polymers and a 0.1% emulsifier, such as PEG, in a 1:1 ethanol: dichloromethane solution at room temperature. As an emulsifier, 80 ml of 0.46% w/w polyvinyl alcohol is progressively mixed with this solution. Before filtering, this is agitated for an hour using a propeller agitator to let the organic solution evaporate. Based on the optimized outcomes of multiple processing factors, such as the polymer ratio, drug:polymer ratio, stirring speed, and emulsifier concentration, the optimal formulation is selected²¹.

Solvent evaporation

Among the polymers utilized to further these mechanisms are ethyl cellulose, Eudragit, and HPMC KM4. To create a homogenous polymer solution, pharmaceuticals are mixed with polymers and dissolved in solutions of ethanol, acetone, or dichloromethane, either alone or in combination. The 100 mL of liquid paraffin is then filled with the solution, and the mixture is spun at 1500 rpm. After forming, the emulsion is heated to 350°C for three hours. Shortly after a stable emulsion forms, all acetone or dichloromethane is completely eliminated, and the resulting cemented microspheres are filtered using passed thru Whatmann filter paper for filtering. The hollow microspheres give the floating and sustained properties²².

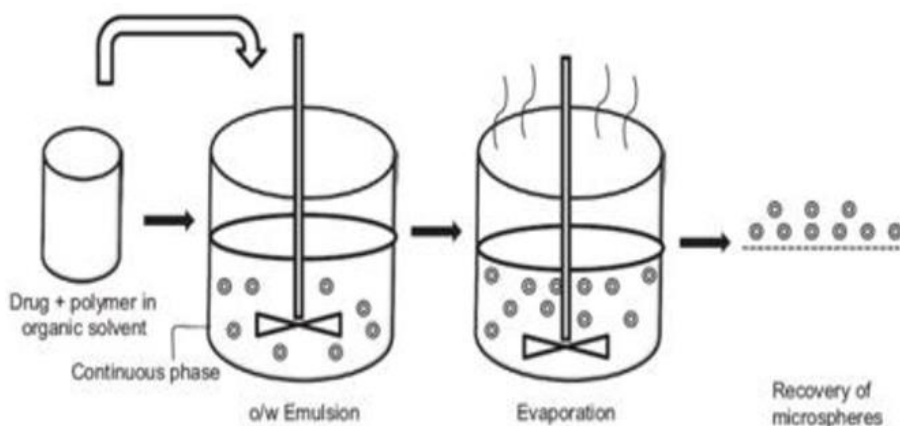


Figure 4: Preparation of microballoons by solvent evaporation method

Characterization of the Optimized Microballoons: -

Determination of bulk density, tapped density and particle density: - Separate portions of the improved formulation (1 g) were added to a graduated measuring cylinder (10 ml) and their respective volumes were recorded. The USP bulk density device was used to tap the graduated measurement cylinder fifty times.

Particle size analysis: - Using an eye piece micrometer that was calibrated, the optical microscopic approach was used to analyze the particle size. A median diameter was computed by measuring the sizes of around 100 particles.

Scanning Electron Microscopy (SEM): - SEM was used to use a scanning electron microscope to characterize the morphology of microballoons. Using double-sided adhesive tape, they were directly mounted onto the SEM sample stub and coated with 200 nm thick gold layer at 0.001 mmHg of decreased pressure²³.

In vitro drug release study: - The in vitro drug release from microballoons has been studied using a USP (United State Pharmacopoeia) basket apparatus. In this study, drug release was investigated at a temperature of $37 \pm 0.5^\circ\text{C}$ using a USP dissolving apparatus type I operating at 100 rpm in distilled water with 0.1 mol HCl (pH 1.2) as the dissolution fluid (900 ml). Spectrophotometric analysis was performed on the withdrawn samples. To keep the sink state, the volume was replenished with the same volume of new dissolving fluid each time²⁴.

Buoyancy percentage: - A suitable quantity of microballoons was added to 900 milliliters of 0.1 N hydrochloric acid. For eight hours, the mixture was agitated in a dissolving apparatus at 100 rpm. The layer of buoyant microballoons was pipetted and filtered after eight hours. By using filtration, the particles in the sinking particulate layer were separated. Both kinds of particles were dried in a desiccator

until their weight remained constant. The microballoon fractions were weighed, and the weight ratio of the floating particles to the total of the sinking and floating particles was used to calculate buoyancy ²⁵.

$$\% \text{ Buoyancy} = [W_f / W_f + W_s] \times 100;$$

Where W_f and W_s are the weights of the floating and settled microspheres.

Stability Studies: - It would be more easy to conduct expedited stability experiments while the product is stored under extreme temperature circumstances, as conducting research at room temperature during storage will take longer. A polyethylene-coated aluminum container with an optimized formulation was used to store the samples for two months at a temperature of 40°C and a relative humidity of 75%. Samples were examined for physical characteristics, drug content, and drug release at the conclusion of the trials.

Release kinetics: - To determine the mechanism of drug release, data from in-vitro release studies were fitted to a variety of kinetic equations ²⁶.

Table 1: Marketed formulations of antidiabetic drug encapsulated microballons

Name of drug	Method used for preparation	References
Metformin	Emulsion solvent evaporation method	²⁷
Theophylline	Ionotropic gelation method.	²⁸
Repaglinide	Solvent evaporation technique	²⁹
Glipizide	Emulsion solvent diffusion technique	³⁰
Glimepiride	Solvent evaporation technique	³¹
Rosiglitazone metformin	Wet granulation method	³²
Nateglinide	Solvent evaporation method.	³³
Silymarin	solvent evaporation techniques	³⁴
Liraglutide	Solvent evaporation method	³⁵
Exenatide	Emulsion method with microfluidic technique	³⁶
Novel Glucagon-like peptide -1 analog (PGLP-1)	Solvent evaporation method	³⁷

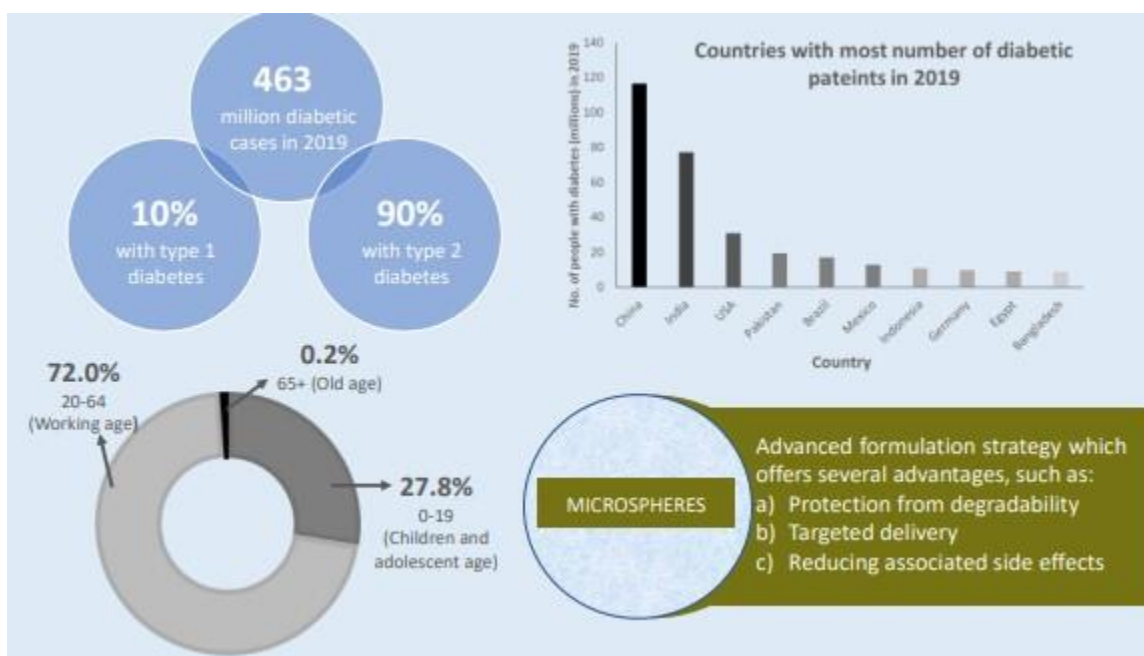


Figure: 5 Graphical representation of use of microballons in treating diabetes

Table 2: List of insulin loaded microballons along with significant outcome

Name of carrier	Method of preparation	Outcome	Reference
Arabinoxylans	Covalent crosslinking by enzymatic reaction.	a) Higher insulin release in the colon region b) Better hypoglycaemic activity	³⁸
PBA-surfacemodified porous PLGA	Water in oil in water double emulsion preparation method	a) Prolonged hypoglycaemic activity b) Scalability and reproducibility due to simplified preparation requirements c) Glucose sensitive release of insulin	³⁹

Methoxypolyethylene glycolhydrazones-4-methoxypolyethylene glycol benzoate	Water in oil in water double emulsion preparation method	a) Glucose-responsive insulin release b) Quick onset of action and for a longer duration of time	⁴⁰
Poly-L-lactic acid	Emulsion-combined precipitation of compressed CO ₂ antisolvent process	Marked hypoglycaemic activity by using inhalation therapy	⁴¹
Glycidyl methacrylate dextran and Concanavalin A	High-speed water-in-oil (W/O) emulsification	a) Glucose-responsive release of insulin maintained for a longer duration. b) Prolonged preservation of bioactivity of insulin	⁴²

CONCLUSION

Diabetes is a dangerous metabolic illness, and in order to reduce the prevalence of diabetes worldwide, cutting edge therapeutic solutions are required. Using microballons could be one way to more effectively administer the therapeutic drug from a formulation standpoint. The review covers some of the most recent studies that use cutting-edge methods for preparing conventional or modified microspheres in order to increase their potential for therapeutic use. the creation of microballons to provide a long-acting carrier system for medications and enable efficient distribution. To provide the maintain release properties, researchers have created resin- and alginate-based microspheres that are loaded with anti-diabetic medications. The extended release of insulin in response to glucose and faster absorption were achieved by the researchers through the use of several carrier systems that preserved bioactivity. Certain microspheres made with arabinoxylans, PLGA, and other materials were able to increase the insulin's hypoglycemic impact. Finally, in creating the microspheres that target diabetes, there may still be some difficulties due to non-uniform size distribution, burst release, lack of repeatability, immunogenicity, etc. To improve the therapeutic and diagnostic efficacy of drug carriers, some recent research has

demonstrated great potential in creating drug carriers with physicochemical and pharmacokinetic characteristics.

Drugs with a short half-life that must be repeated at shorter intervals and are absorbed from the upper portion of the gastrointestinal tract are administered in gastroretentive dose forms. These are useful in lowering the quantity of medication that must be given as well as the dose interval. The majority of gastroretentive drug delivery strategies have demonstrated encouraging outcomes for the long-term administration of antidiabetic medications. Experiments conducted in vivo have demonstrated that controlling the rate and degree of drug release is not a challenging task. The GRDFs of anti-diabetic medications have been the subject of extensive research, although there is still room for more study. Diverse methodologies have been employed in the production of sustained drug delivery of antidiabetic drugs.

References

1. Campbell RK. Type 2 diabetes: where we are today: an overview of disease burden, current treatments, and treatment strategies. *Journal of the American Pharmacists Association*. 2009 Sep 1;49(5):S3-9.
2. Reed J, Bain S, Kanamarlapudi V. A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. *Diabetes, Metabolic Syndrome and Obesity*. 2021 Aug 10;3567-602.
3. Vigersky RA. An overview of management issues in adult patients with type 2 diabetes mellitus. *Journal of Diabetes Science and Technology*. 2011 Mar;5(2):245-50.
4. Sherwin R, Felig P. Pathophysiology of diabetes mellitus. *Medical Clinics of North America*. 1978 Jul 1;62(4):695-711.
5. Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: blood pressure goals, choice of agents, and setting priorities in diabetes care. *Annals of internal medicine*. 2003 Apr 1;138(7):593-602.
6. Hansen LJ, de Fine Olivarius N, Siersma V, Drivsholm T, Andersen JS. Individualised treatment goals in diabetes care. *Scandinavian journal of primary health care*. 2004 Jun 1;22(2):71-7.
7. Borzecki AM, Berlowitz DR. Management of hypertension and diabetes: treatment goals, drug choices, current practice, and strategies for improving care. *Current hypertension reports*. 2005 Nov;7(6):439-49.

8. Deruiter JA. Overview of the antidiabetic agents. *Endocrine Pharmacotherapy Module*. 2003;3(3):45-50.
9. Subramani K, Pathak S, Hosseinkhani H. Recent trends in diabetes treatment using nanotechnology. *Digest Journal of Nanomaterials & Biostructures (DJNB)*. 2012 Jan 1;7(1).
10. Zhao R, Lu Z, Yang J, Zhang L, Li Y, Zhang X. Drug delivery system in the treatment of diabetes mellitus. *Frontiers in bioengineering and biotechnology*. 2020 Jul 29;8:880.
11. Kumar R, Saha P, Sarkar S, Rawat N, Prakash A. A Review On Novel Drug Delivery System. *IJRAR-International Journal of Research and Analytical Reviews (IJRAR)*. 2021 Jan;8(1):183-99.
12. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith A. Floating dosage forms: An in vivostudy demonstrating prolonged gastric retention. *J Control Release*. 1998;55:3–12.
13. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. In vivo evaluation of riboflavin containingmicroballoons for floating controlled drug delivery system in healthy human volunteers. *J Control Release*. 2003;93:39–47
14. Kawashima Y., Niwa T., Takenchi H., Hino T., Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. *J Pharm Sci*. 81; 1992: 135-140.
15. Pujara N.D., Patel N.V., Thacker A.P., Raval B.K., Doshi S.M., Parmar R.B. Floating microspheres: a novel approach for gastro Retention. *World journal of pharmacy and pharmaceutical sciences*. 1 (3); 2012: 872-895.
16. Dhole AR., Gaikwad PD., Bankar VH., Pawar SP. A Review on Floating Multi particulate Drug Delivery System- a Novel Approach to Gastric Retention. *IJPSRR*. 6 (2); 2011: 205-211.
17. Somwanshi SB., Dolas RT., Nikam VK., Gaware VM., Kotade KB., Dhamak KB., Khadse AN. Floating Multiparticulate Oral Sustained Release Drug Delivery System. *J.Chem.Pharm Res*. 3 (1); 2011: 536-547.
18. Saneshan V, Krishna Kanth VSVSP. Preparation and in vitro evaluation of microballoon drug delivery system of Telmisartan. *Int. J. Pharm. Sci. and Drug Res*. 2013; 5(4): 141-145.
19. Sharma Megha, Kohli Seema, Dinda Agnimitra. In vitro and in vivo evaluation of Repaglinide loaded floating microspheres prepared from different viscosity grades of HPMC polymer. *Saudi Pharm. J*. 2015; 23: 675-682.
20. Kumar R, Kamboj S, Chandra A, Gautam PK, Sharma VK. Microballoons: An advance avenue for gastroretentive drug delivery system-A review. *Pharmaceutical and Biosciences Journal*. 2016 Jul 18:29-40.
21. Joshi VK, Jaimini M. Microballons drug delivery system: A review. *AJPRD*. 2013; 1(1): 7 –17

22. Porwal A, Swami G, Saraf SA. Preparation and evaluation of sustained release microballoons of propranolol. DARU: Journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2011;19(3):193.
23. Chandrakala V, Saral AM. Quality by design approach in formulation of bioadhesive levodopa microspheres. Int J of Pharmacy and Pharm Sci. 5 (4); 2013: 172-178.
24. Yadav VK, Kumar B, Prajapati SK, Shafaat. Design and evaluation of mucoadhesive microspheres of repaginate for oral controlled release. Int J of Drug Delivery. 3; 2011: 357-370.
25. Yadav A, Jain DK. Gastroretentive microballoons of metformin: Formulation Development and Characterization. J of adv Pharma Tech and Res. 2 (1); 2011: 51-56.
26. Aphale S, Shinde S, Dhat S, Bagul U, Saluja J. Development and evaluation of hollow microspheres of Clarithromycin as a gastroretentive drug delivery system using eudragit polymers. Int J of Pharma and Bio Sci. 2 (3); 2011: 344-355.
27. Yadav A, Jain DK. Formulation and evaluation of gastroretentive floating microballoons of anti diabetic drug. Asian J Pharm Life Sci. 2011 Mar;1(2):101-12.
28. Yachawad RD. *Development and evaluation of theophylline microballoons drug delivery system* (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).2012
29. Rani G, Nagaraju R, Rao TL. Formulation and evaluation of floating microballons of repaglinide. World J. Pharm. Res.. 2016 Jul 13;5:859-72.
30. Tripathi M, Radhika PR, Sivakumar T. Formulation and evaluation of glipizide hollow microballoons for floating drug delivery. Bull Pharm Res. 2011;1(1):67-74.
31. Shah RR, Shah RS, Vakhariya RR. Glimepiride Micro balloons: A Novel Approach for Bioavailability Enhancement by Gastro-Retentive Floating Drug Delivery System. Research Journal of Pharmaceutical Dosage Forms and Technology. 2017;9(4):183-6.
32. Puneeth KP. *Development and Evaluation of Gastroretentive Drug Delivery System for an Anti Diabetic Drug* (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).2010
33. Wathore SA, Pandhare YL, Pophalkar PB, Kadam CY. formulation and evaluation of intragastric floating drug delivery system of antidiabetic drug. World Journal of Pharmaceutical Research Vol 8, Issue 9, 2019.
34. Thati S. *Formulation and Evaluation of Floating Microspheres of Silymarin for Enhanced Bioavailability* (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).

35. Wu J, Williams GR, Branford-White C, Li H, Li Y, Zhu LM. Liraglutide-loaded poly(lactic-co-glycolic acid) microspheres: Preparation and in vivo evaluation. *Eur J Pharm Sci.* 2016;92:28- 38. doi:10.1016/j.ejps.2016.06.018
36. Zhai J, Ou Z, Zhong L, Wang YE, Cao LP, Guan S. Exenatide-loaded inside-porous poly(lactic-co-glycolic acid) microspheres as a long-acting drug delivery system with improved release characteristics. *Drug Deliv.* 2020;27(1):1667-1675.
37. Ruan S, Gu Y, Liu B, et al. Long-Acting Release Microspheres Containing Novel GLP-1 Analog as an Antidiabetic System. *Mol Pharm* 2018;15(7):2857-2869.
38. Martínez-López AL, Carvajal-Millan E, Sotelo-Cruz N, et al. Enzymatically cross-linked arabinoxylan microspheres as oral insulin delivery system. *Int J Biol Macromol.* 2019;126:952-959.
39. Zhao F, Wu D, Yao D, et al. An injectable particle-hydrogel hybrid system for glucose-regulatory insulin delivery. *Acta Biomater.* 2017;64:334-345. D
40. Yu J, Wang Q, Liu H, et al. Glucose-Responsive Microspheres as a Smart Drug Delivery System for Controlled Release of Insulin. *Eur J Drug Metab Pharmacokinet.* 2020;45(1):113-121.
41. Lin X, Kankala RK, Tang N, et al. Supercritical Fluid-Assisted Porous Microspheres for Efficient Delivery of Insulin and Inhalation Therapy of Diabetes. *Adv Healthcare Mater.* 2018;8(12):1800910.
42. Yin R, He J, Bai M, et al. Engineering synthetic artificial pancreas using chitosan hydrogels integrated with glucose-responsive microspheres for insulin delivery. *Mater Sci Eng C Mater Biol Appl.* 2019;96:374-382.