MICROBALLOONS: A NOVEL APPROACH TO MITIGATE DIABETES

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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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{6,7}

List of Antidiabetic Agents

\textbf{Alpha-Glucoside Inhibitors}
Acarbose, Miglitol Biguanides Metformin, Phenformin Glitazones (Thiazolidinediones) Rosiglitazone, Pioglitazone,Troglitazone

\textbf{Insulin and Insulin Analogue Sulfonylureas}
First-Generation Sulfonylurea: Tolazamide, Tolbutamide, Acetohexamide, and Chloropropamide.

\textbf{Second-Generation Sulfonylurea}
Glyburide, Glipizide, And Glimepride Glinides (Meglitinides) Repaglinide, nateglinide, mitiglinide.\textsuperscript{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 targets\(^9\)-\(^{10}\). In recent times, novel drug delivery systems, or NDDSs, have gained popularity because of 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 diseases\(^11\).

**Microballoons: 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 procedure\(^12\). 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 container\(^13\). Pharmaceuticals with site-specific absorption from the upper gastrointestinal tract that have low bioavailability could be designed as floating drug delivery systems to maximize absorption\(^1\). 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 shelf.
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\textsuperscript{14-15}.

**Advantages of microballoons**

- 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.
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\textsuperscript{18,19}.

Figure 1: Pictorial representation of microballons

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.\textsuperscript{20}

![Spray drying diagram](image)

**Figure 3: Preparation of microballs 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 selected\textsuperscript{21}.

**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 properties\textsuperscript{22}. 

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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 pressure.

**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±0.5°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 time.

**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.

\[
\% \text{ Buoyancy} = \left\{ \frac{W_f}{W_f + W_s} \right\} \times 100;
\]

Where Wf and Ws 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

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Method used for preparation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Emulsion solvent evaporation method</td>
<td>27</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Ionotropic gelation method.</td>
<td>28</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Solvent evaporation technique</td>
<td>29</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Emulsion solvent diffusion technique.</td>
<td>30</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Solvent evaporation technique</td>
<td>31</td>
</tr>
<tr>
<td>Rosiglitazone metformin</td>
<td>Wet granulation method.</td>
<td>32</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Solvent evaporation method.</td>
<td>33</td>
</tr>
<tr>
<td>Silymarin</td>
<td>solvent evaporation techniques</td>
<td>34</td>
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<tr>
<td>Liraglutide</td>
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<tr>
<td>Exenatide</td>
<td>Emulsion method with microfluidic technique</td>
<td>36</td>
</tr>
<tr>
<td>Novel Glucagon-like peptide -1 analog (PGLP-1)</td>
<td>Solvent evaporation method</td>
<td>37</td>
</tr>
</tbody>
</table>
Table 2: List of insulin loaded microballons along with significant outcome

<table>
<thead>
<tr>
<th>Name of carrier</th>
<th>Method of preparation</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
</table>
| 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        |
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
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.


28. Yachawad RD. Development and evaluation of theophylline microballoons drug delivery system (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).2012


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


34. Thati S. Formulation and Evaluation of Floating Microspheres of Silymarin for Enhanced Bioavailability (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).


