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Floating Drug Delivery Systems of Repaglinide for Gastro-Retentive Controlled Release: A Comprehensive Review

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A B S T R A C T

Diabetes Mellitus is a serious metabolic disorder characterized by persistent hyperglycemia. Repaglinide manages post-operative hyperglycemia, but its effectiveness is limited by its half-life of one hour and its bioavailability of 56%, so it requires frequent doses. The floating drug delivery system (FDDS) provides a powerful gastroretentive solution. By floating in stomach fluids, FDDS extends the period of gastric residence and ensures a stable release of drugs near the intestinal absorption window. This study explores water-based polymers, effervescent agents, design quality, and emerging 3D printing technologies, optimizing the bioavailability of Repaglinide FDDS and improving patient compliance.

Key Words: *Repaglinide, FDDS, Gastro-Retentive, Diabetes Mellitus.*

1. Introduction

1.1 Overview of Diabetes Mellitus and Its Global Burden

Persistent hyperglycemia brought on by decreased insulin production, insulin resistance, or both characterises diabetes mellitus (DM), a chronic metabolic disease. [1, 2] The disease's worldwide burden has risen to concerning levels. [3] According to the 11th edition of the International Diabetes Federation (IDF) Diabetes Atlas, 589 million people worldwide between the ages of 20 and 79—or 11.11% of the adult population—are expected to have diabetes in 2024. [4] By 2050, this epidemiological trajectory is predicted to increase to 853 million cases. Additionally, there are still a lot of diagnostic gaps; in 2024, around 42.8% of cases (251.7 million individuals) were untreated, greatly increasing the risk of macrovascular and microvascular problems. [5–7]

1.2 Need for Oral Controlled Release Drug Delivery Systems

Conventional immediate-release formulations frequently result in variable plasma drug concentrations, even though the oral route is still the preferred modality for drug delivery due to patient compliance and cost-effectiveness. [9, 8]
These "peak-and-trough" pharmacokinetics put patients at risk for both pre-dose hyperglycaemic rebounds and post-dose hypoglycemia shocks in chronic diseases such as Type 2 diabetes. [10, 11] The active pharmaceutical ingredient (API) is released at a fixed, continuous rate using controlled-release drug delivery devices. [12]
This process considerably lowers the frequency of doses and lessens side effects by stabilising plasma concentrations within the limited therapeutic window. [13]

1.3 Introduction to Gastro-Retentive Drug Delivery Systems

Highly varying gastrointestinal transit durations typically compromise the clinical effectiveness of traditional oral controlled-release formulations. [15, 14]
By purposefully extending the gastric residence time (GRT) of the dose form, Gastro-Retentive Drug Delivery Systems (GRDDS) get beyond this physiological barrier. [16, 17] GRDDS guarantee a continuous, measured release of the solubilised medication exactly close to the upper intestine absorption window by staying localised in the stomach. [19, 18]

1.4 Concept and Advantages of Floating Drug Delivery Systems

One particularly successful kind of GRDDS is Floating Drug Delivery Systems (FDDS). [20, 21] With a bulk density that is strictly lower than that of stomach fluids (about 1.004 g/cm3), they function on the principle of buoyancy. [22] This prevents the system from being expelled via the pyloric sphincter and keeps it stranded on the surface of the stomach contents. [23, 24] Targeted bioavailability increase, controlled steady-state drug release, defence against catastrophic dosage dumping, and decreased risk of localised mucosal irritation are some of the benefits of FDDS. [25, 26]

1.5 Introduction to Repaglinide and Its Therapeutic Importance

A powerful, short-acting oral insulin secretagogue of the meglitinide family, repaglinide is frequently used to treat postprandial hyperglycemia in Type 2 diabetes [27]. It works by preventing ATP-dependent potassium channels in pancreatic beta cells, which causes rapid insulin exocytosis. [28] Repaglinide's remarkable short biological half-life of around an hour and poor absolute oral bioavailability of 56% limit its therapeutic relevance despite its effectiveness. A laborious multi-daily dosage schedule is required because of its quick hepatic elimination via CYP3A4 and CYP2C8 enzymes. [29, 30] A sensible clinical approach to extend Repaglinide's therapeutic activity, lower dosage frequency, and enhance patient compliance is to formulate it as an FDDS. [31, 32]

2. Gastro-Retentive Floating Drug Delivery Systems

2.1 Principle and Mechanism of FDDS

Archimedes' concept serves as the operational basis for FDDS. The solid dosage form must keep its density below 1.004 g/cm3 to maintain float. [33, 34] The system's peripheral hydrophilic polymers quickly hydrate when it encounters acidic stomach juice, creating a very viscous gel barrier. [35] Carbon dioxide (CO2) gas is produced in effervescent systems by the reaction of implanted alkaline bicarbonates with penetrated gastric acid. [36, 37] These gas bubbles are trapped by the gel matrix, which causes the device to expand volumetrically and lose density, resulting in instant buoyancy. [38, 39]

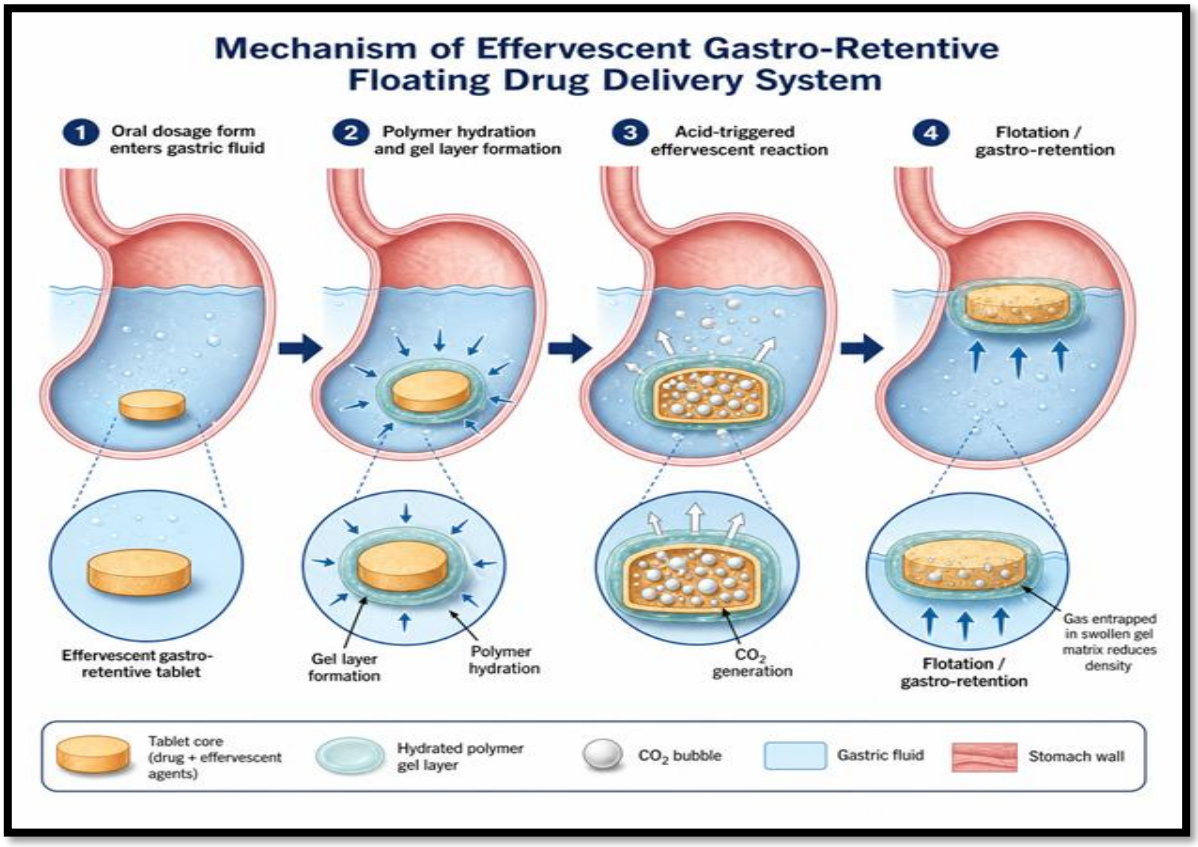

Figure.1: Schematic representation of the mechanism of effervescent gastro-retentive floating drug delivery systems, illustrating polymer hydration, CO2 generation, and subsequent flotation.

2.2 Classification of Floating Systems

FDDS is systematically categorised using two major domains: [40]

Non-Effervescent Systems: These systems only acquire buoyancy by the spontaneous swelling of matrix-forming polymers (like Hydrodynamically Balanced Systems) or by incorporating naturally porous, low-density components like hollow microspheres. (41)

Effervescent Systems: Gas-generating agents, such sodium bicarbonate, are employed to chemically create CO2 when stomach acid comes into contact with these dynamic formulations. (42, 43) Active gas trapping considerably shortens the "floating lag time." [44, 45]

2.3 Advantages and Limitations of Floating Systems

FDDS significantly raises absolute bioavailability by extending the absorption window in the upper small intestine. [41] They are very helpful for weakly basic drugs that only dissolve in acidic environments. [13]

However, FDDS have several disadvantages, including the possibility that their buoyant orientation may be compromised if the patient is completely supine and the requirement that there be enough stomach fluid to start polymer hydration and effervescence. [35]

3. Repaglinide and Its Suitability for FDDS

3.1 Physicochemical and Pharmacokinetic Properties

Repaglinide is a very lipophilic weak acid with a pKa of around 3.9. [15] It falls within Class II of the Biopharmaceutics Classification System (BCS), which denotes significant membrane permeability but extremely poor water solubility. [44] When consumed orally, it binds strongly (>98%) to plasma proteins and rapidly undergoes oxidative biotransformation in the liver. [5]

3.2 Short Biological Half-Life and Poor Bioavailability

The primary challenge is the chronopharmacology of repaglinide therapy. Because of their one-hour half-life, immediate-release formulations cause a rapid increase in plasma concentration followed by a rapid decline. [31]

This pharmacokinetic uncertainty forces patients to follow stringent pre-prandial dosage schedules. [45] Missed doses result in severe hyperglycemia, whereas delayed meals can induce severe, sometimes deadly hypoglycemia. [41]

3.3 Need for Prolonged Gastric Retention and Controlled Release

An FDDS is used to retain repaglinide continuously in the stomach in order to overcome its numerous biological limitations. [1] Before the medicine is progressively metered into the duodenum, sophisticated polymer matrices can fully dissolve the drug in the acidic stomach environment, which acts as a stable dissolving vessel. [35]

By completely removing dangerous concentration spikes and replacing them with a steady-state plasma profile that matches basal insulin secretion, this continuous input ultimately enhances bioavailability and clinical safety. [28]

4. Polymers and Excipients Used

4.1 Hydrophilic Polymers: HPMC, Carbopol, and Sodium Alginate

The primary matrix formers are hydroxypropyl methylcellulose (HPMC) grades with high viscosity, such as K4M, K15M, and K100M [1]. A thick, looping hydrogel barrier that tightly regulates fluid penetration and physical gas trapping is created when HPMC is submerged in the stomach and hydrates.[36] Carbopol (Carbomer): Carbopol 934P and 974P are synthetic acrylic polymers with potent volumetric swelling characteristics. [23]

In addition to offering strong secondary mucoadhesive properties to stabilize the pill if buoyancy fluctuates, they absorb a lot of water to lower the bulk density. [13] The formation of floating microspheres with multiple units requires the natural anionic polysaccharide sodium alginate.[12] Ionotropic gelation rapidly cross-links calcium chloride (CaCl2) and sodium alginate to form rigid, very stable spherical matrices that effectively trap the drug.[28]

4.2 Emerging Natural Polymers

Recent formulation research has highlighted the biocompatibility of plant-based exudates. [18] Moringa oleifera gum has demonstrated exceptional performance as a rate-retardant polymer in Repaglinide FDDS [40]. High concentrations of this natural gum rapidly and massively gel in simulated stomach contents, creating a robust diffusion barrier that can sustain drug release for 12 hours. [34]

4.3 Gas-Generating Agents

Sodium bicarbonate (NaHCO3) is the most often used gas-forming excipient for effervescent FDDS [16]. When gastric hydrochloric acid enters the pill, it reacts with NaHCO3 to form CO2 gas. [25] Empirical research indicates that a well-calibrated NaHCO3 concentration (often between 10 and 15%) guarantees instantaneous lift while avoiding catastrophic gel matrix rupture. [8]

5. Formulation and Evaluation of Floating Tablets

5.1 Methods of Preparation

Repaglinide's strong hydrophobicity causes it to dissolve too slowly when raw crystals are immediately crushed. [24] To make solid dispersions, formulators often combine Repaglinide with hydrophilic carriers like PEG-6000 using a solvent kneading technique. [39] This transforms the crystalline drug into a highly soluble amorphous complex, which is geometrically combined with HPMC, Carbopol, and NaHCO3 before being crushed. [3] To produce multiple-unit microspheres, ionotropic gelation or the emulsion solvent diffusion technique are frequently employed. [13]

5.2 Pre-Compression and Post-Compression Evaluation

Pre-compression mixtures must have excellent flowability (Angle of Repose, Carr's Index). [44] To verify chemical compatibility, FTIR and Differential Scanning Calorimetry (DSC) are employed. [25] For instance, the preservation of Repaglinide's distinctive endothermic melting peak at around 215.6 °C in the formulation confirms full drug-excipient compatibility. [16] After compression, tablets are evaluated for hardness (optimised between 6.3 and 7.1 kg/cm2 to balance structural integrity and fluid infiltration). [30]

5.3 Floating Lag Time, Total Floating Time, and In Vitro Drug Release

The survivability of Repaglinide FDDS is characterized by rigid in vitro buoyancy measurements: [35] Floating Lag Time (FLT): HPMC/Carbopol formulations optimised with 14% NaHCO3 frequently offer a very fast FLT of less than 1-2 minutes, safely exceeding stomach emptying. [11]

Total Floating Time (TFT): Strong hydrogel barriers allow these monolithic tablets to maintain structural integrity and buoyancy for 24 to 34 hours. [24] In vitro dissolution profiles show that repaglinide release from optimal HPMC matrices is compatible with the Higuchi model. [11] The mathematical application of the Korsmeyer-Peppas exponential equation demonstrates non-Fickian (anomalous) transport, showing that a closely linked equilibrium between fluid diffusion and polymer chain relaxation controls drug release. [2]

6. Recent Research and Future Prospects

6.1 Recent Advancements in Repaglinide FDDS

Current research heavily relies on statistical Quality by Design (QbD) methods such as Box-Behnken and Central Composite Designs to quantitatively tune HPMC and NaHCO3 ratios for flawless repeatability. [12] For example, recent studies have successfully mapped the effects of ethyl cellulose, HPMC, and NaHCO3 on drug release patterns and microparticle buoyancy using Box-Behnken designs. [26]

Table 1: Observed values of responses for Box-Behnken design optimisation of Repaglinide floating microparticles.

Formulation Code	HPMC (%)	EC (%)	NaHCO3 (mg)	Buoyancy (%)	Drug Release at 10h (%)
F1	1.5	1.0	50	67.00	81.12
F3	1.0	1.0	100	68.66	88.12
F7	1.0	1.5	150	75.66	88.12
F8	1.5	2.0	150	78.33	81.67
F12	1.0	1.5	50	66.66	86.47

The therapeutic effectiveness of these systems has been confirmed by in vivo research. [34] Advanced calcium silicate-based floating granules of Repaglinide administered to animal models demonstrated a prolonged GRT exceeding 6 hours in contrast to immediate-release commercial capsules, resulting in an incredible 3.8-fold increase in relative systemic bioavailability. Furthermore, natural matrices utilising Moringa oleifera gum have shown virtually perfect sustained release profiles (93.9% over 12 hours) and physical stability throughout three months of accelerated testing procedures [36]. [43]

6.2 Future Opportunities: Nanotechnology and 3D Printing

Repaglinide gastro-retentive systems of the future are rapidly integrating with nanotechnology and additive fabrication. [6]

Nanocrystals: Scientists have developed "smart" Repaglinide nanocrystals with a mean diameter of only 71.31 nm, utilizing precision microfluidic processors. [23] This massive increase in specific surface area significantly improves saturation solubility. [31] By generating a noticeably extended hypoglycemic response at far lower therapeutic concentrations (0.5 mg/kg), these nanocrystals minimize the hepatic metabolic burden in vivo. [35]

The computational creation of physical voids directly into the macroscopic architecture of the dosage form is made possible by Fused Deposition Modelling (FDM) in 3D printing. [28] By creating specially designed internal mesh networks (such as 0.6 x 0.6 mm) that capture ambient air during production, 3D-printed devices offer instantaneous, fail-safe buoyancy that is entirely independent of chemical effervescence. [20] This paradigm shift promises unprecedented personalization of Repaglinide medicine for the treatment of Type 2 Diabetes Mellitus. [7]

Conclusion

The formulation of Repaglinide as FDDS largely overcomes its biopharmaceutical limitations. Conventional forms of immediate release cause dangerous "peak and trough" pharmaceutical fluctuations. By keeping the drug in the stomach using polymer matrices and gas producing agents, FDDS gives a continuous stable release that imitates the basal insulin secretion. This prevents concentration spikes and ensures system bioavailability in a safe manner. The future integration of nanocrystals and 3D printing promises unbreakable flotation and personalized dosage. Finally, Repaglinide FDDS provides a superior and lasting release profile that maximizes clinical safety, efficacy and long-term patient compliance.

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