RESEARCH PAPER

Gastroretentive Floating Tablets for Anticonvulsant Delivery: A Review of Formulation Strategies and Sustained Release Mechanisms

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ABSTRACT

This review examines a rate-controlled drug delivery system for anticonvulsant agents that are mainly absorbed in the stomach at acidic pH 1-3. Short gastric residence time reduces bioavailability and causes variations in drug levels, which is a key issue for anticonvulsants requiring steady plasma concentrations to prevent seizures. Floating sustained-release tablets were designed using buoyancy to extend stomach retention and provide continuous drug release. The formulations use release-controlling polymers like HPMC K15, NaCMC, Carbopol and Xanthan gum, along with sodium bicarbonate and citric acid as gas-generating agents. Lactose and ethyl cellulose were also included. The review covers tablet preparation, evaluation methods, and effects of processing variables on release profiles. FTIR and DSC studies confirmed no significant drug-polymer interactions. This floating approach improves gastric retention, enhances bioavailability, and maintains consistent drug action. It offers a practical strategy for anticonvulsant therapy, enabling prolonged effect and reduced dosing frequency for better management of epilepsy and neuropathic pain.

Keywords: Rate-controlled, Sustained-release, Gastric retention time, HPMC K15, NaCMC, Xanthan gum, Carbopol, Sodium bicarbonate.

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Introduction:

Epilepsy

"Epilepsy is one of the most common neurological disorders of the brain affecting the central nervous system." It is a chronic, non-communicable neurological disorder characterized by a predisposition to generate recurrent, unprovoked seizures.[1]

This neurological condition is the second most common. Since it impacts roughly 50 million individuals globally.[2]

Genetic susceptibility, anatomical brain abnormalities, metabolic diseases, infections, immune-mediated illnesses, and unidentified reasons are all part of the multifactorial aetiology of epilepsy. Head trauma, brain tumors, brain infections such as meningitis or encephalitis, stroke, birth defects, and occasionally even changes in blood sugar or sodium levels can all cause epilepsy.[3]

Epilepsy classification based on seizure types present in the patient

1. Focal Epilepsy: Characterized by focal seizures Also called as partial seizures. They are originate from aspecific localized area of cerebral hemisphere These type of seizures caused by structural lesions (trauma), stroke, infection, genetic factors, abnormal and excessive neuronal discharge, metabolic causes, or be of unknown etiology. Example: Temporal lobe epilepsy and Fronatal lobe epilepsy.

Types of Focal Seizures

a) Focal Aware Seizures (Simple Partial Seizures)
b) Focal Impaired Awareness Seizures(Complex Partial)
c) Focal to Bilateral Tonic-Clonic Seizures

2.Generalized Epilepsy: A class of epileptic disorders known as generalized epilepsy occurs when seizures begin in one focal area and spread to both cerebral hemispheres at the same time. It is a significant subtype of epilepsy and is usually linked to bilateral, extensive neuronal network involvement.

Types of Generalized Epilepsy

- Absence Seizures
- Tonic-Clonic Seizures (GTCS)
- Myoclonic Seizures
- Atonic Seizures
- Tonic Seizures

3.Combined Generalized and Focal Epilepsy: Patients have both focal and generalized seizures. Seen in conditions like Dravet syndrome and Lennox-Gastaut syndrome.

4.Unknown Epilepsy: Insufficient information to determine if epilepsy is focal or generalized.[4][5]

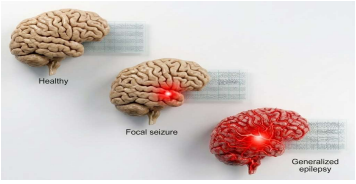

Fig.Types of epilepsy

Diagnosis and Treatment
Identification and Management of Epilepsy

Diagnosis
1.Clinical history : pqpostictal phase, triggers, aura, and description of the seizure.
2.EEG : Identifies focal or widespread discharges; if not, video-EEG is used.
3.MRI : Better than CT, it detects structural causes.
4.Labs : Toxicity screen to rule out mimics, glucose, and electrolytes.

Treatment:
1.Pharmacological: narrow-spectrum AEDs for focal if verified; broad-spectrum for generalized, unknown, or combined. e.g.Topiramate, lamotrigine, levetiracetam, and valproate are common.
2.Non-pharmacological: VNS, ketogenic diet, and epilepsy surgery for focal cases resistant to drugs.
3.Lifestyle: Stress reduction, trigger avoidance, and good sleep hygiene.

Limitations of Drug Delivery Systems for Treatment of Epilepsy

Despite advances in anticonvulsant therapy, conventional drug delivery systems face several limitations that compromise therapeutic outcomes in epilepsy.

- Blood-Brain Barrier (BBB) Penetration
- Narrow Therapeutic Index and Dose-Dependent Toxicity
- Poor Patient Compliance
- Inadequate Site-Specific Delivery
- Variable Gastrointestinal Absorption
- Lack of Sustained Release for Seizure Control
- Difficulty in Dose Individualization

These limitations have driven research into novel delivery approaches including floating tablets, mucoadhesive systems, nanoparticles, intranasal delivery, and implantable devices to enhance BBB transport, sustain release, improve targeting, and reduce systemic toxicity.

Gastroretentive Drug Delivery Systems (GRDDS): Floating Tablets for Treatment of Epilepsy

Drug delivery refers to the method or process of administering a pharmaceutical compound to produce a therapeutic effect in humans or animals. Among various drug administration routes, the oral route is

the most preferred due to its cost-effectiveness and ease of use. The primary objective of a drug delivery system is to achieve and sustain therapeutic drug concentrations at the target site, releasing the drug at a predefined rate based on physiological requirements over the desired treatment duration.[6] Developing systems that can prolong and modulate gastric emptying provides a strategic advantage for formulations requiring extended gastric retention compared to standard dosage forms.[7] Floating drug delivery systems, also known as hydrodynamically balanced systems, are low-density formulations that remain buoyant on gastric fluid without affecting normal gastric emptying for an extended period. They are particularly advantageous for drugs with poor solubility or stability in intestinal media. While the system floats on gastric contents, the drug is released in a controlled manner. After complete drug release, the system is evacuated from the stomach. This mechanism improves gastric retention time and minimizes fluctuations in plasma drug concentrations.[8] The management of epilepsy and neuropathic pain relies heavily on anticonvulsant therapy. Formulating these agents as floating drug delivery systems overcomes challenges associated with their absorption profiles. This approach facilitates sustained release, leading to improved bioavailability and reduced variability in plasma drug concentrations.[18]

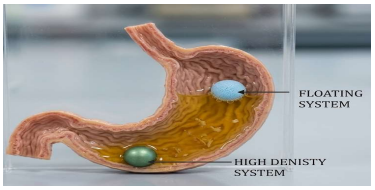

Fig.Gastroretentive Drug Delivery Systems (GRDDS)

Mechanism of Floating Tablets

Floating drug delivery systems are low-density formulations that remain buoyant on gastric fluid without affecting gastric emptying. They are classified as non-effervescent or effervescent systems. On contact with gastric fluid, effervescent types generate CO_2 via reaction of carbonates with acid, which is entrapped in a gel matrix, reducing density. Non-effervescent types use swellable polymers like HPMC that form a gel barrier and entrap air. While buoyant, the tablet releases drug in a controlled manner at or above the absorption window, followed by evacuation after complete drug release.[20]

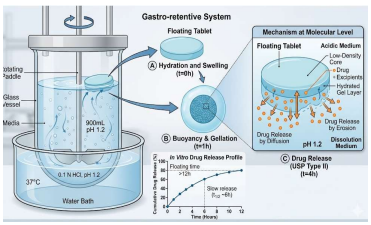

Fig 3. Mechanism of drug release from Floating tablet

Advantages

- Prolonged Gastric Retention
- Sustained Release Profile
- Reduced Dosing Frequency
- Bypass Intestinal Instability
- Decreased Plasma Fluctuations

Disadvantages

- Acid-unstable drugs
- Food dependent
- Absorption window limited
- First-pass effect needed
- Solubility/stability issues

Techniques for Creating FDDS

1. Effervescent technique: Acids and bicarbonates react to produce carbon dioxide, which gives gastric fluid buoyancy.
2. Direct compression method: Without changing the drug's structure, tablets are compressed straight from powder blends.
3. Ionotropic gelation technique: To create floating gel systems, polymers like sodium alginate are crosslinked with calcium ions.
4. Wet granulation technique: binders are used to turn

powders into granules, which are then dried or ground.
5. Spray drying method: By quickly evaporating the solvent, drug dispersions are sprayed into a drying chamber to create floating particles.
6. Method of solvent evaporation: This process creates low-density, hardened systems that can float in stomach fluid.
7. The melt solidification technique: Creates buoyant dosage forms by dispersing drugs in molten carriers and cooling them.[11][16]

Basic components of Floating Drug Delivery Systems for Treatment of Epilepsy

Drug: Antiepileptic medications (AEDs), which are chosen according to the type of seizure and patient characteristics, are the mainstay of pharmacological treatment for epilepsy. Because they work well for both focal and generalized seizures, broad-spectrum AEDs are frequently chosen. Among these, tonic-clonic, absence, and myoclonic generalized seizures can be effectively treated with valproic acid; however, its use is restricted due to teratogenicity and metabolic side effects. Lamotrigine, which primarily acts through sodium channel inhibition, is frequently used because of its good tolerability and safety during pregnancy. While topiramate offers wide efficacy but may have cognitive side effects, levetiracetam has gained importance due to its favorable safety profile and low drug interactions.
On the other hand, narrow-spectrum AEDs, like phenytoin and carbamazepine, are primarily used to treat focal seizures by blocking sodium channels, though they may exacerbate some forms of generalized seizures. In general, monotherapy is used to start treatment, followed by dose titration or combination therapy if necessary, with careful consideration of patient-specific factors, safety, and efficacy.

Polymers(Matrix forming agents):
These regulate the rate of drug release, gel formation, and swelling. HPMC grades K4M, K15M, and K100M are hydrophilic and quickly swell to create a gel barrier. Better buoyancy and slower release are associated with higher viscosity.
Carbopol 934P/971P is an anionic polymer that depends on pH. Increases mucoadhesion, gel strength, and gastric pH. Utilized for synergy with HPMC.
Polyethylene oxide, or PEO, has a high capacity for swelling and creates a robust hydrogel. Excellent for high-dose medications.
Natural polymers include sodium alginate, guar gum, and xanthan gum. Use Ca2+ or acid to induce swelling and in situ gelation.

Effervescent components/Gas-generating agents:
When the tablet comes into contact with 0.1 N HCI, it produces CO2 to provide buoyancy.
The most prevalent is sodium bicarbonate ($NaHCO_3$). Reacts with acid, traps CO2 in the gel matrix, and causes the tablet to float.
A different, slower method of releasing CO2 is calcium carbonate.
Citric acid / Tartaric acid: 2-10% w/w,added with NaHCO3 to ensure CO2 generation even in patients with low gastric acid. Also acts as pH modifier.

Fillers and Diluents:
Fillers and diluents in floating tablets modify compressibility, density, and bulk of the formulation. Microcrystalline cellulose (MCC) pH 101/102 is used at 10–30% and is favored for anticonvulsant drugs due to its low density, strong compatibility, and ability to promote wicking and swelling while also increasing tablet hardness. Lactose is water-soluble and forms pores during hydration, but because it increases tablet density, its use in FDDS is limited to less than 20% to maintain buoyancy. Dibasic calcium phosphate (DCP) is dense and non-swelling; if used at more than 10%, the tablet may sink, so it is generally avoided or used in very low amounts. Mannitol is water-soluble, has low density, and provides a pleasant

mouthfeel, making it an excellent diluent for effervescent floating systems.

Lubricants & Glidants:
Lubricants and glidants are incorporated to improve powder flow and tablet ejection during compression. Magnesium stearate is used at 0.5–1%; however, it is hydrophobic and may retard water penetration into the matrix, so its concentration is kept low in FDDS. Talc, used at 1–2%, is less hydrophobic than magnesium stearate and provides good lubrication with minimal impact on hydration. Aerosil, or colloidal silicon dioxide, is used at 0.2–0.5% to enhance flow properties without affecting buoyancy. The primary role of these excipients is to prevent sticking and picking during compression, but they must not form a water-impermeable coat that would hinder tablet hydration and floating.

Release Modifiers / Channeling Agents:
Release modifiers and channeling agents are added to modulate drug diffusion and control gel porosity in the swollen matrix. Water-soluble agents like lactose and mannitol dissolve in gastric fluid to create micro-channels, which facilitate uniform drug release and allow escape of CO_2 in effervescent systems. For non-effervescent FDDS, insoluble polymers such as ethyl cellulose and Eudragit RL/RS are used to form a low-density matrix that sustains release. Sodium lauryl sulfate, a surfactant used at 0.5–2%, improves the wetting and dissolution of poorly soluble drugs like carbamazepine, thereby enhancing release rate without compromising buoyancy.

1.Pre-formulation Parameters
Preformulation testing is the initial stage in the logical creation of dosage forms for a medication. It can be characterized as an examination of a drug's chemical and physical characteristics of material, both by itself and in conjunction with excipients. The purpose of preformulation testing is to produce data that the formulator can use to dosage forms that are bioavailable, stable, and mass-producible. Physicochemical characteristics could offer a justification for the formulation's design and justify the necessity of molecular modification, or verify that there aren't any major obstacles to the compound's growth. Thus, the purpose of preformulation is to determine a new drug's essential physicochemical properties material,ascertain the profile of its kinetic release rate and determine whether it is compatible with various excipients.Therefore, preformulation analyses of the drug sample obtained include color, taste, compatibility studies, solubility analysis, and melting point determination.

2.Bulk Density and Tapped Density:
About 2 g of powder blend from each formulation was introduced into a 10 mL measuring cylinder after breaking agglomerates. The initial volume was noted as bulk volume. The cylinder was then tapped continuously until no further change in volume was observed, and the final tapped volume was recorded. Bulk density (BD) and tapped density (TD) were calculated using the following equations:

Bulk density=Mass/Initial bulk volume

Tapped density=Mass/Tapped volume

3.Compressibility Index (Carr's Index):
Carr's compressibility index was determined to evaluate the flow properties of the powder blend using bulk density and tapped density values. It was calculated using the following formula:

Carr's index=Tapped density–Bulk densityx100

4.Hausner's Ratio:
Hausner's ratio was calculated from the bulk density and tapped density to determine flowability of the powder blend using the formula:

Hausner's ratio= Tapped density/Bulk density

A Hausner's ratio value below 1.25 indicates good flow properties,

whereas values above 1.25 indicate poor flow characteristics**.**

Preparation method Direct compression

Sustained release anticonvulsant floating tablet made by direct compression, all the ingredients, API, Matrix forming polymers, sodium bicarbonate, Citric acid, magnesium stearate, talc and lactose weigh accurately for 10 tablets in each batch and triturate using mortar pestle until the blend become uniform then sieve the blend from 40 no mesh. Weigh 250 mg for each tablet compression, API 100 mg in concentration, all the tablet after compression place in air tight container for further study.[15][17]

Evaluation of Floating Tablets for Treatment of Epilepsy

1.Diameter and Thickness

The thickness of individual tablets measured using Vernier calliper, which permits accurate measurements and provides information of the variation between tablets. 10 tablets were randomly selected from each batch.Diameter and thickness measured individually using Vernier calipers and mean values calculated.

2.Weight Variation

Weigh 20 tablets individually on an analytical balance.Calculate average weight from total weight of 20 tablets.Compare individual tablet weight with average weight.

3.Content uniformity

Test to ensure that each tablet in a batch contains the active ingredient within a narrow range around the label claim.Select 10 tablets randomly from the batch.Assay each tablet individually using a validated analytical method like UV, HPLC.Calculate % of label claim for each tablet.[17]

4.Hardness

Hardness of the tablets was determined using the Monsanto hardness tester and the Average values were calculated.it indicate the mechanical strength to withstand handling,packaging and transport of tablets.[19]

5.Friability

The friability of the tablets carried out in a Roche friabilator. Friability done with the 20 tablets adjust the time at 4 min and speed at 25 rpm.[19]

Friability (%)=W1-W2/W1 x 100

Where, W1=Initial Weight of Tablets
W2=Final Weight of Tablets

6.Determination of swelling index

Swelling index is the percentage increase in weight of a tablet due to uptake of aqueous fluid and subsequent hydration of hydrophilic polymers. It quantifies the extent of swelling and gel layer formation when the tablet contacts dissolution medium.[14][17] Tablets were weighed initially as W1 and placed in 0.1 N HCl at 37±0.5°C. At 1, 2, 4, 6, 8, and 12 h, each tablet was removed, blotted to remove surface water, and weighed as W2.

Swelling Index (%) = [(W2 – W1) / W1] × 100

Where, W1= Initial weight of tablet
W2=Weight of the tablet after swelling

7.Floating lag time (Buoyancy time)

The floating lag time was used to calculate the in vitro buoyancy and how long the developed tablets floated, In short,The tablets were put in a 100 mL beaker with 0.1 N.HCl (pH 1.2). The media was maintained in a stagnant state and370 C was the constant temperature. The amount of time needed for the tablet to float and rise to the surface was established.as the floating durations and floating lag time were visually noted.[12]

8.In-vitro drug release study

The USP II tablet dissolution test apparatus was used for in vitro release investigations at 60 rpm. For twelve hours, 900 milliliters of 0.1 N HCL served as the dissolution medium. The temperature was kept at 37 ± 0.5°C. At prearranged intervals, a 5 ml sample was taken out and replaced with an equivalent volume of new dissolution fluid that had been equilibrated at the same temperature. One ml of that five

ml sample was taken out and added to a ten ml volumetric flask along with ten ml of 0.1 N HCL. Analyze the medication right away using absorbance. Calculate % cumulative drug release using calibration curve method.[13]

Conclusion:

Floating gastroretentive tablets represent a promising rate-controlled drug delivery
approach for anticonvulsants that exhibit narrow absorption windows in the stomach. By prolonging gastric residence time through buoyancy, these systems address key limitations of conventional therapy such as poor bioavailability, fluctuating plasma levels, and frequent dosing these are all critical issues in epilepsy management where steady drug concentrations are essential to prevent seizures. Formulations based on hydrophilic polymers like HPMC K15, NaCMC, Carbopol, and xanthan gum, combined with gas-generating agents such as sodium bicarbonate and citric acid, successfully achieve sustained drug release over 8–12 h. Overall, FDDS offers a practical, patient-friendly strategy to enhance therapeutic efficacy of anticonvulsants. It improves bioavailability, reduces dosing frequency, and minimizes plasma level fluctuations, leading to better seizure control and improved compliance in patients with epilepsy and neuropathic pain.

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