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Gastro- Retentive floating tablets: A promising strategy for improving dapsone therapeutic efficacy.

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ABSTRACT:
This review explores the formulation and development of floating tablets for gastro-retentive drug delivery systems (GRDDS), focusing on their ability to prolong gastric retention and enhance the therapeutic efficacy of drugs with narrow absorption windows. The article discusses key components of floating tablet systems, mechanisms of buoyancy, materials, methods, and evaluation parameters. The significance of such systems for improving therapeutic outcomes and patient compliance is highlighted, along with the limitations and challenges faced in formulation.Dapsone is a widely used antimicrobial agent, suffers from limitations such as poor solubility, short gastric residence time, and variable bioavailability, leading to suboptimal therapeutic outcomes. Gastro-retentive drug delivery systems (GRDDS), particularly floating tablets, offer a promising approach to overcoming these challenges by prolonging gastric retention and enhancing drug absorption. This review explores the formulation strategies, mechanisms, and advantages of gastro-retentive floating tablets for Dapsone. Key aspects such as polymer selection, effervescent and non-effervescent floating mechanisms, pharmacokinetic benefits, and in vitro/in vivo evaluation methods are discussed. Additionally, formulation challenges and future prospects, including the potential for advanced polymer technologies and nanocarriers, are highlighted. By improving gastric retention and controlled drug release, floating tablets could significantly enhance the therapeutic efficacy of Dapsone, making them a promising alternative to conventional oral dosage forms.

Keywords: Gastro-retentive system, floating tablets, controlled release, bioavailability, gastric retention, formulation, evaluation, hydrodynamic balance, buoyancy, drug delivery.

I. INTRODUCTION:

Gastro-Retentive Drug Delivery Systems (GRDDS) are designed to retain a drug in the stomach for an extended period, improving its bioavailability and ensuring a more controlled release.[1-2]They are particularly beneficial for drugs with a narrow absorption window, poor solubility in intestinal fluids, or those that degrade in the colon. Floating drug delivery systems (FDDS), one of the most researched GRDDS, offer prolonged gastric retention by maintaining buoyancy in the stomach's gastric fluid, ensuring the drug remains in the optimal region for absorption.[3-4]

Various formulation-related factors such as polymer types (nonionic, cationic, and anionic polymers), polymer composition in dosage form, viscosity grade, molecular weight of the polymer, and drug solubility can affect the quality of the gastroretentive dosage form. Moreover, the physicochemical nature of excipients plays an important role in various GRDDS.[5-6]

Why Floating Tablets? FDDS, especially floating tablets, maintain their position at the surface of gastric fluids, ensuring sustained release. This system is suitable for drugs like Dapsone or similar actives, which require extended exposure in the stomach to maximize absorption and therapeutic effectiveness. Floating tablets are advantageous because they:[7-8]

- Enhance bioavailability.
- Reduce dosing frequency.

1.2 Advantages of Gastro-retentive Drug Delivery Systems (GRDDS) over Conventional Drug Delivery Systems

Gastro-retentive drug delivery systems (GRDDS), such as floating tablets, mucoadhesive systems, or expandable systems, offer several advantages over conventional drug delivery systems, particularly for drugs with specific absorption windows in the stomach or upper small intestine.

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Advantages of GRDDS:

1. **Prolonged Gastric Retention:**

a) Enhances drug absorption for drugs absorbed in the stomach or upper gastrointestinal tract (GIT).

b) Improves bioavailability of drugs with narrow absorption windows.

2. **Reduced Dosing Frequency:**

a) Maintains a steady drug release profile, reducing the need for frequent dosing.

b) Enhances patient compliance, especially for chronic therapies.

3. **Minimized Drug Wastage:**

a) Reduces pre-systemic metabolism or degradation of drugs sensitive to intestinal pH or enzymes.

4. **Improved Targeting:**

a) Ensures localized drug release in the stomach, beneficial for treating gastric ulcers, infections (e.g., H. pylori), and gastric cancers.

5. **Reduced Side Effects:**

a) Sustained drug release minimizes fluctuations in drug plasma levels, lowering the risk of adverse effects.

6. **Enhanced Solubility:**

a) Suitable for drugs that are poorly soluble at higher pH levels but dissolve well in acidic environments.

1.3 Comparison of GRDDS vs. Conventional DDS in GIT

Below is a comparison of **Gastro-retentive DDS** and **Conventional DDS** showing their location and release profiles in the gastrointestinal tract:

1. **Conventional DDS**:

a) Moves through the GIT rapidly.

b) Drug release occurs throughout the GIT, reducing efficiency for stomach-targeted drugs.

2. **GRDDS**:

a) Retains in the stomach due to mechanisms like floating, swelling, or adhesion.

b) Provides prolonged drug release in the stomach.

1.4 Important Gastrointestinal (GI) Physiological Aspects for Designing GRDDS

Understanding the anatomy, physiology, and transit time of the GI tract is essential for designing effective gastro-retentive drug delivery systems (GRDDS). Key factors include stomach anatomy, motility, pH variations, gastric emptying time, and the absorption mechanism. Below is a summary of these aspects, along with a table for transit times of different dosage forms.

Table 1. Key Anatomical and Physiological Features of the GI Tract

Segment	Length	Diameter	Presence of Villi	Absorption Mechanism	pH	Constituents	Transit Time of Food
Mouth	15 cm	Varies	No	No absorption	7 (neutral)	Saliva, enzymes (amylase)	Seconds to 1 min
Esophagus	25 cm	2 cm	No	No absorption	7 (neutral)	Mucus	~10 seconds
Stomach	25 cm	10-12 cm	No	Passive diffusion	1-3 (acidic)	HCl, pepsin, mucus	2-4 hours
Small Intestine	6 m	3-4 cm	Yes	Active transport, diffusion	6-7.5 (slightly basic)	Enzymes, bile, mucus	3-5 hours
Duodenum	25 cm	4 cm	Yes	Active transport, diffusion	6-6.5	Bile, pancreatic enzymes	30 minutes
Jejunum	2.5 m	3.5 cm	Yes (dense)	Active transport, diffusion	6.5-7	Enzymes, mucus	2 hours

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Ileum	3.5 m	3 cm	Yes (sparse)	Active transport, diffusion	7-7.5	Enzymes, mucus	2-3 hours
Large Intestine	1.5 m	6-7 cm	No	Passive diffusion	7-8 (neutral-basic)	Bacteria, water, electrolytes	10-48 hours

Table 2. Transit Time of Different Dosage Forms Across GIT

Dosage Form	Stomach	Small Intestine	Large Intestine
Liquids	30 minutes	1-2 hours	12-48 hours
Tablets (Immediate Release)	2-4 hours	3-5 hours	12-48 hours
Tablets (Sustained Release)	4-8 hours	5-8 hours	24-72 hours
Capsules	2-4 hours	3-5 hours	12-48 hours
Floating Dosage Forms	Retained for 6-8 hours	3-5 hours	12-48 hours

Table 3. Different approaches to increase gastric residence time presented in a structured format: [9]

Approach	Description
High-density systems	Designed to sink to the bottom of the stomach, resisting gastric emptying due to their weight.
Bioadhesive or mucoadhesive systems	Adhere to the gastric mucosa to prolong their residence time in the stomach.
Swelling and expanding systems	Swell or expand upon contact with gastric fluids, preventing passage through the pylorus.
Superporous hydrogels	Absorb large amounts of gastric fluid and swell rapidly, remaining in the stomach for a longer time.
Ion exchange resins	Use the ionic environment of the stomach to control drug release and extend gastric retention.
Bioadhesive liposomal systems	Liposomes coated with bioadhesive materials to stick to the stomach lining, increasing retention time.
Raft-forming systems	Form a viscous cohesive gel or 'raft' that floats on gastric fluids to prolong drug release.
Gas-generating systems	Produce gas bubbles to reduce system density, allowing the dosage form to float on gastric fluids.
Low-density systems (Floating systems)	Maintain buoyancy in the gastric contents by being less dense than gastric fluid, prolonging residence.

1.5 Overview of Gastro-Retentive Drug Delivery Systems:

1. Types of GRDDS: [10-11]

- **Floating systems**: These are designed with low-density polymers that allow the dosage form to float on gastric fluids.
- **Mucoadhesive systems**: Adhere to the gastric mucosa to prolong the retention time.
- **Expandable systems**: Expand in the stomach to prevent passage through the pylorus.

Among these, floating systems are preferred for drugs like Dapsone that benefit from increased residence time in the upper gastrointestinal (GI) tract.

A. Effervescent Floating Systems

Mechanism:

- Use effervescent agents like sodium bicarbonate and citric acid.
- When in contact with gastric fluid, CO_2 is generated, entrapped in the dosage form, and makes it buoyant.

Examples:

- Floating tablets and capsules.

Advantages:

- Prolonged gastric retention.
- Easy formulation.

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B. Non-Effervescent Floating Systems
Mechanism:
- Use swellable polymers (e.g., HPMC, chitosan) that form a gel layer upon hydration, reducing density.
- The dosage form floats without gas generation.

Examples:
- Hydrogel-based floating systems.

Advantages:
- Better control over drug release.
- Long retention time.

C. Raft-Forming Systems
Mechanism:
- Upon contact with gastric fluids, form a viscous gel-like structure that floats and acts as a barrier.

Examples:
- Alginate-based antacid preparations.

Advantages:
- Effective for gastroesophageal reflux disease (GERD).

D. Floating Microspheres
Mechanism:
- Low-density spherical particles prepared using polymers like Eudragit float on gastric fluid.

Advantages:
- Uniform drug dispersion.
- Sustained release.

E. Floating Beads
Mechanism:
- Hydrogel beads containing air or gas pockets float in gastric fluid.

Advantages:
- Simple preparation.
- Applicable for multiple drugs.

2. Benefits of Floating Tablets: [12-14]
- Prolong gastric retention.
- Controlled drug release.
- Improved drug solubility and bioavailability for poorly soluble drugs.

1.6 Mechanism of Floating Tablets:

Floating drug delivery systems rely on the hydrodynamic principle of buoyancy. Tablets are formulated with ingredients like low-density polymers (e.g., hydroxypropyl methylcellulose or HPMC), which allow the tablet to float on gastric fluid. The tablet absorbs water, swells, and releases the drug gradually while remaining buoyant.[15-16]

Mechanism Illustrated:
- **Step 1**: After ingestion, the tablet comes in contact with gastric fluids.
- **Step 2**: The low-density polymers form a gel-like layer that traps air, allowing the tablet to remain afloat.
- **Step 3**: The drug is released slowly from the matrix as the polymers hydrate, ensuring sustained release.[17-19]

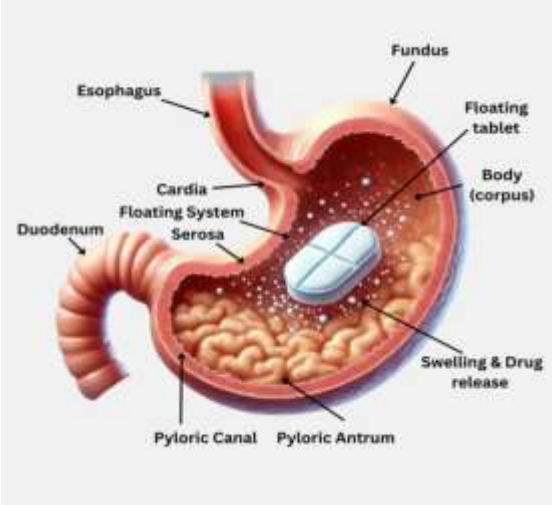

Fig 1. Cross-section of the stomach with the floating tablet

1.7 Concept of Absorption Windows

An **absorption window** is the specific region in the gastrointestinal (GI) tract where a drug demonstrates optimal absorption due to favorable physicochemical, enzymatic, or physiological conditions. Drugs outside this window may exhibit suboptimal absorption, leading to reduced bioavailability.

Features of Absorption Windows:
1. **Location-Specific**:
   - Stomach: Acidic drugs or those needing acidic conditions (e.g., aspirin).
   - Small Intestine: Neutral or slightly basic pH favors most drugs (e.g., antibiotics).
   - Colon: Limited absorption but suitable for certain sustained-release drugs.

2. **Time-Limited**:
   - The transit time in the GI tract restricts how long a drug is exposed to its absorption window (e.g., stomach: 2-4 hours, small intestine: 3-5 hours).

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3. **Dependence on Solubility and Permeability**:
- Drug solubility (affected by pH) and intestinal permeability (via passive diffusion or transporters) determine absorption efficiency.

Examples:
- **Levodopa**: Best absorbed in the proximal intestine.
- **Riboflavin (Vitamin B2)**: Requires active transport in the small intestine.

1.8 Need for GRDDS to Increase Bioavailability and Challenges in Drug Absorption Without GRDDS:

1. **Short Gastric Retention Time**:
- Drugs with a narrow absorption window leave the stomach or upper intestine before full absorption.
2. **Poor Solubility in Alkaline pH**:
- Drugs requiring acidic conditions may dissolve poorly in the intestine.
3. **Enzymatic Degradation**:
- Drugs unstable in intestinal fluids lose efficacy (e.g., proteins and peptides).
4. **Fluctuations Due to Food**:
- Variability in gastric emptying and pH due to food can affect drug release and absorption.

1.9 Why is a Floating System Needed for Dapsone?

Dapsone, used to treat leprosy and various skin conditions, has a narrow absorption window in the upper gastrointestinal tract. As a drug that degrades in the colon and has variable absorption, it is ideal for a gastro-retentive system. A floating tablet ensures that Dapsone is retained in the stomach, where it can be absorbed efficiently, providing better therapeutic effects and reducing dose frequency.[20-21]

Table 4. Dapsone, focusing on its use in dermatology, pharmacokinetics and pharmacodynamics, indications, and dosage.[22-23]

1. Dapsone Use in Dermatology	
Primary Dermatologic Uses	Dapsone is widely used for treating dermatologic conditions due to its anti-inflammatory and immunomodulatory effects.
Dermatitis Herpetiformis:	First-line treatment for this chronic blistering skin condition, often linked to gluten sensitivity
Leprosy	Bacteriostatic effects help in treating Mycobacterium leprae as part of multi-drug therapy.
Acne Vulgaris and Acneiform	Reduces inflammation in certain acne-related conditions.
Pemphigus and Pemphigoid	Used in treating autoimmune blistering disorders like bullous pemphigoid
Other Inflammatory Skin Disorders	Sometimes prescribed for pyodermagangrenosum, lupus erythematosus, and erythema elevatumdiutinum.
2. Pharmacokinetics	
Absorption	Well absorbed orally, peak plasma levels occur 2-8 hours after administration
Distribution	Widely distributed in tissues (skin, liver, kidneys), volume of distribution: 1.5 L/kg.
Metabolism	Metabolized in the liver via N-acetylation (monoacetyldapsone) and N-hydroxylation, producing active and toxic metabolites
Elimination Half-Life:	Long half-life of 10-50 hours, allowing once-daily dosing
Excretion	Primarily excreted through kidneys, some undergoes enterohepatic recirculation.
3. Pharmacodynamics	
Mechanism of Action	Inhibits dihydropteroate synthase, interfering with bacterial folic acid synthesis, providing antibacterial and anti-inflammatory effects

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Anti-inflammatory Properties	Suppresses neutrophil activity and reduces reactive oxygen species production, helpful in inflammatory skin conditions.
4. Indications for Use	
Dermatitis Herpetiformis:	First-line therapy.
Leprosy	Used in multidrug therapy to prevent resistance.
Acne Vulgaris	Sometimes used topically for mild to moderate acne.
Pemphigus and Pemphigoid	Adjunct treatment for autoimmune blistering diseases.
Other Skin Infections:	May be prescribed for pyodermagangrenosum and cutaneous lupus erythematosus.
5. Dosage	
Oral Dosage for Adults	Dermatitis Herpetiformis: 50-300 mg daily; Leprosy: 100 mg once daily
Topical Formulation	5% gel applied once or twice daily for acne
Pediatric Dosage	1-2 mg/kg daily, adjusted based on weight and response.
Dose Adjustments	Required for liver disease patients and slow acetylators to reduce toxicity risk
6. Safety and Monitoring	
Side Effects	Hemolysis (especially in G6PD deficiency), methemoglobinemia, nausea, headache, liver toxicity
Monitoring	Regular blood counts and liver function tests recommended monitoring for hematologic and hepatic side effects.

Table 5. Dapsone's usage in various dermatological conditions, including the dosage, induction.[24-25]

Condition	Dose	Induction/Treatment Duration
Dermatitis herpetiformis	Oral: 50-200 mg daily	Start at lower dose (50 mg) and titrate up based on response. Long-term treatment may be needed.
Leprosy	Oral: 100 mg daily	Part of a multi-drug regimen (usually 6-12 months for paucibacillary, 12-24 months for multibacillary).
Acne vulgaris	Topical: 5% gel twice daily	Continue treatment for at least 12 weeks for noticeable improvement.
Bullous pemphigoid	Oral: 50-150 mg daily	Dose may be adjusted based on the severity of the disease; often combined with prednisone.
Linear IgA bullous dermatosis	Oral: 50-200 mg daily	Dose adjusted based on clinical response; taper slowly after symptoms improve.
Erythema elevatumdiutinum	Oral: 50-100 mg daily	Treatment may last for several months to achieve remission.
Pyodermagangrenosum	Oral: 50-200 mg daily	Dose adjusted based on clinical response; may be used in combination with other immunosuppressive agents.
Sweet's syndrome	Oral: 50-100 mg daily	Short-term use until resolution of symptoms, typically within weeks to months.
Lupus erythematosus (cutaneous)	Oral: 50-150 mg daily	Induction with a higher dose, then maintenance dose; treatment duration varies.
HIV-associated conditions (PCP prevention)	Oral: 50-100 mg daily or 100 mg three times weekly	Long-term prophylaxis, especially in patients with low CD4 counts.
Malaria prophylaxis	Oral: 100 mg weekly, often in combination with other drugs	Duration depends on the exposure risk.

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Brown recluse spider bites	Oral: 50-100 mg daily	Typically used for 1-2 weeks.
Autoimmune neutropenia	Oral: 50-100 mg daily	Treatment duration varies based on the severity of the condition.

1.10 Ideal Drug Candidate for GRDDS

Drugs that benefit from gastro-retentive drug delivery systems (GRDDS) typically possess specific physicochemical and pharmacokinetic properties. GRDDS enhances their therapeutic efficacy by increasing gastric retention and providing controlled drug release.

Characteristics of Ideal Drug Candidates

1. **Narrow Absorption Window**:
- Drugs primarily absorbed in the stomach or upper small intestine.
- Example: Levodopa, Riboflavin.
2. **Poor Solubility at Alkaline pH**:
- Drugs that dissolve better in acidic environments.
- Example: Ciprofloxacin, Dapsone.

3. **Local Gastric Action**:
- Drugs intended to act locally in the stomach.
- Example: Antacids, Misoprostol.

4. **Stability in Acidic pH**:
- Drugs that are chemically stable in the acidic environment of the stomach.
- Example: Aspirin.

5. **Low Absorption from the Colon**:
- Drugs with minimal or no absorption beyond the small intestine.
- Example: Furosemide.

6. **Short Half-Life**:
- Drugs with a short elimination half-life benefit from sustained release.
- Example: Metformin.

1.11 Regional Variability in Gastrointestinal (GI) Absorption

Gastrointestinal absorption varies significantly across different regions of the GI tract due to anatomical, physiological, and biochemical differences. These variations influence drug dissolution, solubility, permeability, and bioavailability, making it essential to consider regional differences when designing drug delivery systems such as GRDDS.

Factors Influencing Regional GI Absorption

1. **pH**
- ✓ Varies across the GI tract, affecting drug solubility:
- ➢ Stomach: Acidic (pH 1-3), ideal for weak acids.
- ➢ Small intestine: Neutral to slightly basic (pH 6-7.5), optimal for most drugs.
- ➢ Colon: Slightly basic to neutral (pH 7-8).

2. **Surface Area and Villi**
- ✓ Small intestine has the largest surface area due to villi and microvilli, facilitating absorption.
- ✓ Colon lacks villi, leading to reduced absorption capacity.

3. **Transit Time**
- ✓ Varies across regions:
- ➢ Stomach: 2-4 hours (fasting) or 4-8 hours (fed state).
- ➢ Small intestine: 3-5 hours.
- ➢ Colon: 10-48 hours.

4. **Enzymatic Activity**
- ✓ Stomach: Pepsin and gastric enzymes digest proteins.
- ✓ Small intestine: Pancreatic enzymes and bile enhance solubility and digestion.
- ✓ Colon: Microbial enzymes act on unabsorbed drugs.

5. **Permeability**
- ✓ Highest in the small intestine due to thin epithelial lining and tight junctions.
- ✓ Decreases in the colon and stomach due to thicker mucus layers and limited transport mechanisms.

1.12 Role of GRDDS in Addressing Regional Variability

Gastro-retentive drug delivery systems (GRDDS) help overcome absorption challenges by:

- **Prolonging Retention in Specific Regions**: Retains drugs in the stomach or upper small intestine to ensure optimal absorption.
- **Stabilizing Drugs in Acidic Environments**: Protects drugs that degrade in alkaline conditions.

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- **Enhancing Bioavailability**: Improves absorption for drugs with narrow absorption windows in the upper GI tract.

II. MATERIALS AND METHODS:

1. Ingredients:

- **Active Drug**: Dapsone (or alternative drug with similar pharmacokinetics).
- **Polymers**: HPMC (Hydroxypropyl methylcellulose), PVP (Polyvinylpyrrolidone), Carbopol, and Sodium alginate.
- Properties: HPMC is responsible for floatation and controlled release. Sodium alginate improves gel formation.
- **Excipients**: Magnesium stearate (lubricant), lactose (filler), and stearic acid (release modifier).[26-28]

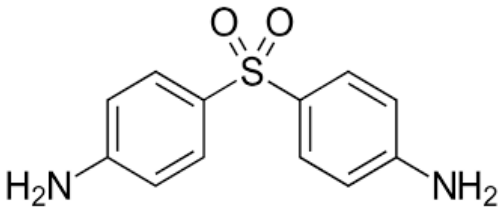
2. Drug Properties:

- **Dapsone**: Hydrophobic, poorly soluble in the intestine, well-absorbed in the stomach.
- Solubility: Poor in water, requiring controlled release for optimal bioavailability.
- Half-life: Long half-life necessitates sustained release for continuous therapeutic effects.[29]

2.2 Dapsone for GRDDS

1. Structure of Dapsone

- **Chemical Name**: 4,4'-Diaminodiphenyl sulfone.
- **Structure**: A sulfone with two amino groups attached to a diphenyl backbone.



Structure of Dapsone

2. Solubility Profile of Dapsone

- **Solubility**:
  - Sparingly soluble in water.
  - Freely soluble in organic solvents like acetone and ethanol.
- **LogP**: ~0.97 (moderate lipophilicity).

3. SAR (Structure-Activity Relationship) of Dapsone

- **Core Structure**: The diphenylsulfone backbone is critical for antimicrobial activity.
- **Substituents**:
  - Amino groups at the para positions are essential for activity against Mycobacterium leprae.
  - Modifications to the sulfone group or aromatic rings can reduce potency.

4. Absorption Window of Dapsone

- **Optimal Absorption**: Proximal small intestine due to its moderate lipophilicity.
- **Challenges**: Limited solubility in alkaline conditions can hinder absorption beyond the duodenum.

2.3 Mechanism of Absorption, Dissolution, Metabolism, and Elimination of Dapsone as a Floating Tablet

Dapsone is a sulfone antibiotic with unique pharmacokinetics, which can be optimized using a floating drug delivery system (FDDS).

1. Dissolution

Floating Tablet Mechanism:

- The floating tablet remains buoyant in gastric fluid due to its low density.
- Prolonged retention in the stomach ensures gradual release of Dapsone.

Dissolution Process:

- The acidic environment of the stomach facilitates the dissolution of Dapsone.
- Polymers in the formulation (e.g., HPMC, Carbopol) regulate the release, ensuring sustained delivery.

2. Absorption

Site of Absorption:

- Dapsone is absorbed primarily in the upper small intestine (duodenum and jejunum), where the conditions are optimal for its absorption.

Mechanism of Absorption:

- Dapsone is a moderately lipophilic drug (logP ~0.97), favoring passive diffusion through the lipid bilayer of intestinal epithelial cells.
- The floating tablet maintains drug concentration near the absorption site for extended periods, enhancing bioavailability.

3. Metabolism

Primary Metabolic Pathway:

- Dapsone undergoes hepatic metabolism predominantly through:

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- **N-acetylation**: Catalyzed by N-acetyltransferase enzymes, forming monoacetylated and diacetylated metabolites.
- **Oxidation**: Mediated by cytochrome P450 enzymes, producing hydroxylamine metabolites.

Significance of Metabolites:
- Hydroxylamine derivatives contribute to the hemotoxic effects (e.g., methemoglobinemia).

4. Elimination
Routes of Excretion:
- **Renal Elimination**:
- Dapsone and its metabolites are primarily excreted through the kidneys.
- Approximately 70-80% of the drug is excreted in urine, mostly as acetylated metabolites.
- **Fecal Elimination**:
- A smaller fraction of the drug is eliminated unchanged in feces.

Half-Life:
- Dapsone has a relatively long half-life of 20–30 hours, which may be further prolonged by the sustained release from a floating tablet.

2.4 Characterization of Dapsone

Characterization is crucial for understanding Dapsone's physicochemical and biological properties, ensuring successful formulation development.

1. Physicochemical Properties
- **Appearance**: White to slightly yellow crystalline powder.
- **Molecular Formula**: $C_{12}H_{12}N_2O_2S$.
- **Molecular Weight**: 248.3 g/mol.
- **Melting Point**: 175–176°C.
- **Log P**: ~0.97 (moderately lipophilic).
- **pKa**: 2.4 (weak acid).

2. Solubility Profile
- **Water Solubility**: Sparingly soluble.
- **Organic Solvents**: Freely soluble in acetone and ethanol.
- **pH Dependence**: Solubility decreases in alkaline pH, making gastric retention beneficial for better dissolution.

3. Thermal Analysis
- **Differential Scanning Calorimetry (DSC)**:
- Identifies melting point, purity, and polymorphism.
- Ensures stability under various temperature conditions.
- **Thermogravimetric Analysis (TGA)**:
- Assesses thermal stability and decomposition.

4. Spectroscopic Studies
- **UV-Vis Spectroscopy**:
- λmax = 295 nm, used for quantitative analysis.
- **Fourier Transform Infrared (FTIR) Spectroscopy**:
- Confirms functional groups like sulfone (-SO_2) and amine (-NH_2).

5. X-Ray Diffraction (XRD)
- Used to determine crystallinity.
- Dapsone shows characteristic peaks indicating a crystalline structure.

6. Micromeritic Properties
- **Bulk Density**: Ensures appropriate flow properties during formulation.
- **Tapped Density**: Evaluates compressibility.
- **Angle of Repose**: Determines flowability.

2.5 Preformulation Studies of Dapsone

Preformulation studies assess the compatibility of Dapsone with excipients and its behavior under different conditions, forming the foundation for successful formulation.

1. Solubility Studies
- **Objective**: Determine solubility in various solvents and media (e.g., simulated gastric fluid).
- **Outcome**: Guides the selection of solubilizers or pH modifiers.

2. Partition Coefficient (Log P)
- Assessed to predict the drug's permeability across biological membranes.

3. Drug-Excipients Compatibility Studies
- **Techniques**: FTIR, DSC, and HPLC.
- **Objective**: Ensure no interaction between Dapsone and excipients that may affect stability or efficacy.

4. Hygroscopicity Studies
- Determines moisture sensitivity.
- Guides storage and handling conditions.

5. Stability Studies
- **Thermal Stability**: Assessed using DSC and TGA.

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- **Photostability**: Evaluates degradation under UV light.
- **Oxidative Stability**: Assessed under oxidative stress conditions.

6. Powder Flow Properties
- **Bulk and Tapped Density**: Helps decide compression parameters.
- **Carr's Index &Hausner Ratio**: Evaluate compressibility and flowability.

7. pH Solubility Profile
- Dapsone's solubility at different pH levels is studied to select the optimal pH for dissolution

8. Partition Coefficient and Permeability
- Determines Dapsone'slipophilicity, guiding formulation strategies to enhance absorption.

9. Polymorphism Study
- Ensures that the selected polymorphic form is stable and bioavailable.

2.6 Formulation Procedure: [30]
- **Granulation**:
- Wet granulation method is used to mix the drug with excipients.
- Binder solution (PVP in water or alcohol) is sprayed on the blend.
- Wet mass is passed through a sieve and dried in a tray dryer at 60°C.

2. **Compression**:
- The granules are compressed using a tablet press with a die, forming tablets of uniform size and weight.

3. **Coating**:
- The tablets may be coated with a polymer film to improve stability and control drug release.

2.7 Types and Technologies of GRDDS

GRDDS technologies are designed to improve gastric retention by employing different mechanisms, such as buoyancy, swelling, adhesion, or density.

1. Floating Drug Delivery Systems (FDDS)
Mechanism: These systems float on gastric fluid due to low density, prolonging gastric retention.
Types:
- **Effervescent Systems**: Generate CO_2 upon contact with gastric fluid (e.g., Sodium bicarbonate + Citric acid).
- **Non-Effervescent Systems**: Use swellable polymers to achieve buoyancy.

2. Swelling or Expanding Systems
Mechanism: Absorb gastric fluid, swell, and increase in size to prevent transit to the small intestine.
Example: Superporous hydrogels.

3. Bio/Mucoadhesive Systems
Mechanism: Adhere to the gastric mucosa, resisting gastric emptying.
Example: Chitosan-based formulations.

4. High-Density Systems
Mechanism: Remain in the stomach by sinking due to a density higher than gastric contents (>2.5 g/cm^3).
Example: Barium sulfate tablets.

5. Superporous Hydrogels
Mechanism: Absorb water rapidly, expanding significantly to prolong gastric retention.
Example: Crosslinked hydrophilic polymers.

2.8 Technologies in GRDDS
Conventional Approaches
1. **Matrix Tablets**: Tablets with polymers (e.g., HPMC) that swell or float.
2. **Floating Microspheres**: Spherical particles with low density, made using polymers like Eudragit.

Recent Advancements
1. **3D Printing**: Enables customized shapes for improved retention.
2. **Layered Delivery Systems**: Combine immediate and controlled release in a single tablet.
3. **Magnetic Systems**: Use an external magnet to retain dosage in the stomach.
4. **Nanoparticles**: Improve targeting and stability in gastric conditions.
5. **Ion-Exchange Resins**: Enable controlled release based on pH or ionic strength.

2.9 Recent Technological Advancements in the Development of GRDDS

The development of Gastro-Retentive Drug Delivery Systems (GRDDS) has evolved significantly with new technologies aimed at enhancing drug retention, bioavailability, and patient compliance. Here are some of the most notable advancements:

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1. 3D Printing Technology

- **Concept**: Enables the fabrication of tailored GRDDS with complex geometries for controlled and sustained drug release.
- **Applications**:
  - Printing multi-layered systems combining immediate and controlled release.
  - Designing swellable or floating structures to optimize gastric retention.
- **Advantages**:
  - Precise dosage control.
  - Customization for patient-specific needs.

2. Superporous Hydrogel Systems (SPHS)

- **Mechanism**: Rapidly absorb gastric fluid to swell and achieve large sizes, preventing gastric emptying.
- **Materials Used**: Hydrophilic polymers like polyacrylamide and alginate.
- **Advantages**:
  - Quick swelling enhances retention time.
  - Suitable for high drug loading.

3. Nanotechnology-Based GRDDS

- **Concept**: Use of nanoparticles to improve drug stability and gastric retention.
- **Types**:
  - **Floating Nanoparticles**: Remain buoyant in gastric fluid.
  - **Mucoadhesive Nanoparticles**: Adhere to gastric mucosa for prolonged action.
- **Applications**: Enhanced targeting and release of drugs like antibiotics and anticancer agents.

4. Magnetic GRDDS

- **Concept**: Incorporates magnetic materials into the dosage form, which can be retained in the stomach using an external magnetic field.
- **Advantages**:
  - Precise localization in the GI tract.
  - Suitable for site-specific drug delivery.

5. Bio/Mucoadhesive Polymers

- **Development**: New polymers like thiolated chitosan and carbopol enhance adhesion to gastric mucosa.
- **Advantages**:
  - Prolonged retention time.
  - Resistance to gastric motility.

6. Floating Pulsatile Drug Delivery Systems

- **Concept**: Combine floating mechanisms with pulsatile release to deliver drugs in bursts at specific time intervals.
- **Applications**: Suitable for drugs with chronotherapeutic requirements (e.g., anti-ulcer drugs).

7. Effervescent Systems with Advanced Polymers

- **Development**: Effervescent systems now incorporate improved polymers like HPMC K4M for controlled gas generation and sustained buoyancy.
- **Advantages**:
  - Prolonged gastric residence.
  - Reduced burst release.

8. Ion-Exchange Resin Systems

- **Mechanism**: Utilize resins that release drugs in response to pH changes in the stomach.
- **Advantages**:
  - Minimized drug wastage.
  - Controlled drug release over an extended period.

9. Layered and Multiparticulate Systems

- **Development**: Dosage forms consisting of multiple layers or coated granules with distinct release profiles.
- **Advantages**:
  - Combined immediate and sustained release.
  - Suitable for drugs requiring dual action.

10. Gas-Filled Floating Systems

- **Concept**: Use gas-filled chambers within the dosage form to enhance buoyancy.
- **Advantages**:
  - Extended floating time (>12 hours).
  - Applicable for low-dose and highly potent drugs.

Table 6. Formulation Aspects of Floating Tablet

Component	Examples	Purpose
Active Pharmaceutical Ingredient (API)	Dapsone	Provides therapeutic effect
Effervescent Agents	Sodium bicarbonate, Citric acid	Generates gas for buoyancy
Polymers	HPMC, Carbopol, Chitosan	Controls drug release

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Binders	PVP, Starch	Ensures tablet cohesion
Fillers	Microcrystalline cellulose, Lactose	Adds bulk to formulation
Lubricants	Magnesium stearate, Talc	Improves flow and prevents sticking
Coating Agents	Eudragit, Ethyl cellulose	Enhances stability and aesthetics
Solubilizers	Polysorbates, Cyclodextrins	Improves drug solubility

III. EVALUATION TESTS:

1. Buoyancy Test:

a) Objective: Measure the floating lag time and total floating duration.

b) Method: Place the tablet in 0.1 N HCl (pH 1.2) and observe the time it takes for the tablet to float (lag time) and the duration it remains floating.

2. Drug Release Profile:

a) Objective: Assess the controlled release of Dapsone over time.

b) Method: Use a USP Type II dissolution apparatus in a simulated gastric fluid (pH 1.2). Samples are collected at regular intervals to measure drug concentration using UV spectrophotometry.

3. Swelling Index:

a) Measure the weight gain of the tablet over time to evaluate swelling, which indicates polymer hydration and gel formation.

4. Stability Study:

a) Perform stability tests under ICH guidelines, evaluating the drug under varying humidity and temperature conditions.

5. In Vitro Drug Release Studies

These studies simulate the drug release process in a controlled environment, mimicking gastric fluids to predict how the drug would behave in the human gastrointestinal tract.Typically performed using USP dissolution apparatus (e.g., paddle or basket type) with simulated gastric fluid at pH 1.2 (without enzymes) as the dissolution medium, maintained at 37°C.

Parameters Measured:

a) **Release Profile**: The rate at which the drug dissolves and is released from the tablet.

b) **Floating Behavior**: The floating lag time and duration the tablet remains buoyant.

c) **Swelling Index**: If the tablet is designed to swell, the extent and speed of swelling are measured.

Significance: Provides a preliminary understanding of the drug release kinetics, stability, and potential efficacy before in vivo testing.

6. In Vivo Drug Release Studies

In vivo studies assess the drug's actual retention and release in the gastrointestinal tract under real physiological conditions.These are typically conducted in animal models or human volunteers. Techniques include:

a) **Radiographic Imaging (X-rays)**: To observe the position and movement of the tablet in the stomach over time.

b) **Gamma Scintigraphy**: Uses radiolabeled tablets to track drug release and retention visually in real-time.

c) **Pharmacokinetic Analysis**: Measures blood plasma concentrations to understand the drug's absorption profile and release rate.

Parameters Measured:

a) **Gastric Retention Time**: The time the tablet remains in the stomach.

b) **Bioavailability**: The proportion of drug absorbed into the bloodstream, reflecting effective delivery.

Significance: Confirms how accurately the in vitro predictions match real-life behavior, allowing for adjustments to enhance efficacy and consistency.

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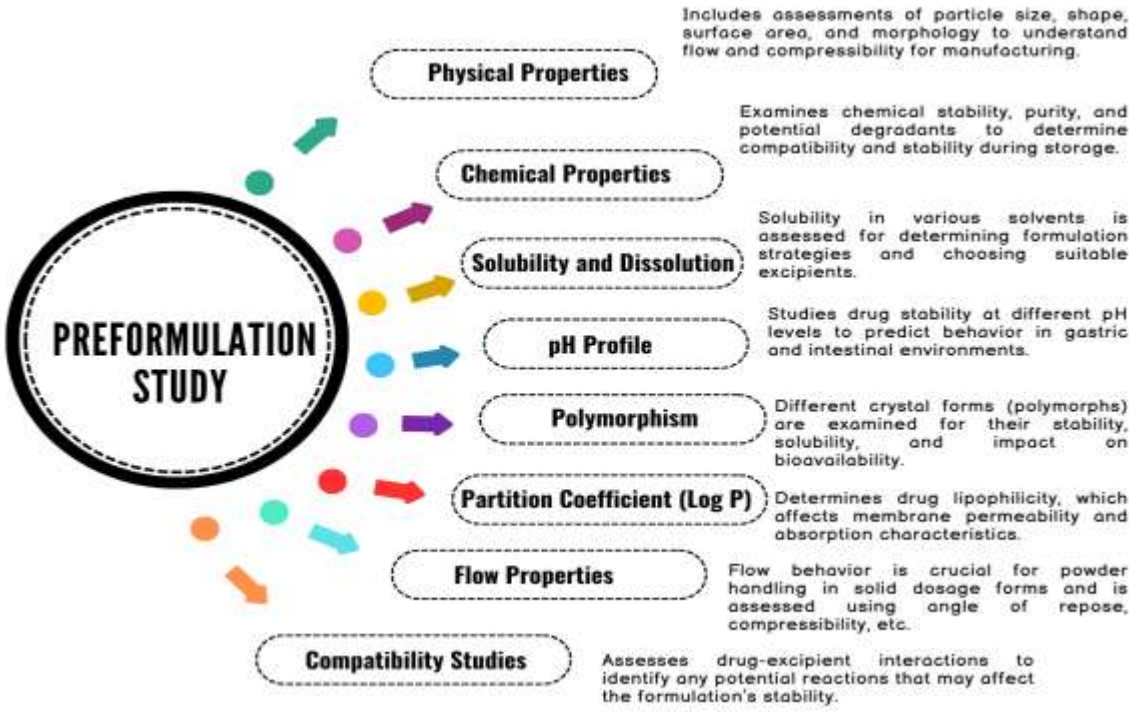

Fig 2. Summary of the primary components typically analyzed in preformulation studies

Table 7. Evaluation parameters for gastro-retentive drug delivery systems (GRDDS):[34-35]

Parameter	Evaluation Method	Expected Outcome
Floating Lag Time	Time taken to float in simulated gastric fluid	< 2 minutes
Total Floating Time	Duration of floating on simulated gastric fluid	> 12 hours
In-vitro Drug Release	Drug release measured over time using dissolution apparatus	Controlled and prolonged release
Swelling Index	Measurement of tablet swelling in gastric fluid	Significant swelling indicating matrix hydration
Buoyancy	Visual observation of buoyancy	Stable and prolonged buoyancy
Weight Variation	Weigh individual tablets and compare	Within pharmacopoeial limits
Hardness	Measure force required to break tablet	Sufficient to withstand handling
Friability	Determine weight loss during handling	< 1% weight loss
Content Uniformity	Analyze drug content in individual units	Uniform content as per standards
Stability Studies	Assess stability under different temperature and humidity conditions	No significant degradation over time

3.2 Limitations: [36-37]

- **Variability in Gastric Emptying**: The effectiveness of floating tablets may vary due to differences in gastric emptying times across patients.

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- **Density Issues**: Achieving consistent low density for floatation can be a challenge during formulation.
- **Stability Concerns**: Some polymers used in floating systems may degrade in acidic conditions over time.

Table 8. Factors affecting the gastroretention time of floating drug delivery systems:[38]

Factor	Description
Density of the System	Systems with lower density than gastric fluids are more likely to float and remain in the stomach longer.
Viscosity of Gastric Contents	Increased viscosity can slow gastric emptying, enhancing retention of floating systems.
Gastric Motility	The rate of gastric contractions can impact how long a dosage form stays in the stomach.
Food Intake	Presence of food can increase gastric retention time due to higher viscosity and changes in gastric motility.
Formulation Characteristics	The composition, particle size, and shape of the dosage form influence its ability to float and adhere.
Buoyancy Mechanism	The type of buoyancy mechanism (e.g., gas-generating, low-density) affects the retention time in the stomach.
Hydration of the System	Hydration affects the swelling and buoyancy properties of the floating system, impacting its retention.
pH of Gastric Contents	Variations in gastric pH can influence the solubility and release profile of the drug, affecting retention.
Drug Properties	Characteristics like solubility and permeability of the drug can impact the efficiency of the delivery system.

Although many GRDDS with various novel fabrication options have been reported for their invitro success, their commercialization success is not significant. A glimpse of a few new candidates together with the old ones is summarized in table no 6.[39-42]

Table 9.Some commercialized gastro-retentive drug delivery systems (GRDDS):

Product Name	Active Ingredient	Formulation Type	Indication
Geoclock	Various	Floating tablet	Various gastrointestinal disorders
Roxatidine	Roxatidine acetate	Floating tablet	Peptic ulcer disease, GERD
Lansoprazole ODT	Lansoprazole	Orodispersible tablet	GERD, peptic ulcers
Lansoprazole DR capsule	Lansoprazole	Delayed-release capsule	Peptic ulcers, GERD
Hydrogel beads	Various (e.g., metformin)	Hydrogel beads	Diabetes management
Sustained Release Metformin	Metformin	Floating beads	Type 2 diabetes
FDC of paracetamol	Paracetamol	Floating tablet	Pain relief
Gastroretentive tablets	Various (e.g., diclofenac)	Floating matrix tablets	Pain and inflammation
AcipHex®	Rabeprazole sodium	Floating tablet	GERD, peptic ulcers
Oxycodone HCl	Oxycodone	Extended-release formulation	Pain management
Zinbryta	Daclizumab	Gastroretentive formulation	Multiple sclerosis

IV. CONCLUSION:

The development of floating tablets as a gastro-retentive drug delivery system offers

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significant advantages for drugs like Dapsone, ensuring prolonged gastric retention, improved bioavailability, and controlled drug release. This review outlines the critical aspects of formulation, the mechanisms behind floating systems, and their potential to enhance therapeutic outcomes. While challenges remain in achieving optimal floatation and stability, floating tablets represent a promising solution for drugs with limited absorption windows.

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