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HERBAL-BASED GASTRORETENTIVE FLOATING MICROBALLOONS: A COMPREHENSIVE REVIEW WITH SPECIAL EMPHASIS ON THUJA LEAVES EXTRACT

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ABSTRACT

Oral drug delivery, while popular for its convenience, faces challenges like rapid gastric emptying and variable absorption. These issues limit the effectiveness of many drugs, especially those that need to be absorbed in the upper gastrointestinal tract. To overcome this, gastroretentive drug delivery systems (GRDDS) were developed. These systems prolong a drug's stay in the stomach, which improves its solubility, absorption, and overall effectiveness. Among these, floating drug delivery systems (FDDS), and specifically microballoons (hollow microspheres), are particularly effective. Their low density allows them to float in gastric fluids, extending the drug's retention time and providing a sustained therapeutic effect. The integration of herbal extracts into new drug forms is a growing trend. Thuja occidentalis, or white cedar, is a medicinal plant rich in bioactive compounds like thujone and flavonoids, giving it antimicrobial, antioxidant, and other health benefits. This review focuses on the development of floating microballoons, examining their formulation and evaluation, while also exploring the potential of using Thuja leaves to create Thuja-based herbal microballoons. The goal is to highlight the opportunities and challenges in this field, encouraging more research into these innovative, natural drug delivery systems.

KEYWORDS: Gastro-retentive drug delivery, Floating microspheres, Micro-balloons, Thuja occidentalis, Herbal formulations, Controlled release.

1. INTRODUCTION

The oral route of drug administration is considered the gold standard in modern therapeutics because of its ease of administration, patient compliance, and cost-effectiveness. Nearly 70–80% of pharmaceutical formulations available in the market are designed for oral use, reflecting its dominance as a drug delivery approach.[1],[2] However, oral administration faces several physiological challenges, including short gastric residence times, variable gastric emptying, fluctuating pH, and enzymatic degradation.[3] These factors often limit drug absorption, especially for drugs with a narrow absorption window restricted to the stomach or upper small intestine.[4] Drugs with poor solubility or instability in gastrointestinal fluids are particularly affected, resulting in reduced therapeutic efficacy and bioavailability. Consequently, novel drug delivery systems have been developed to overcome these barriers and improve oral drug performance.

One of the most promising strategies is the use of gastro-retentive drug delivery systems (GRDDS). GRDDS are designed to extend the residence time of drug formulations in the stomach, thereby ensuring prolonged drug release and absorption at the desired site.[5] Prolonging gastric retention enhances drug solubility, maintains steady plasma concentrations, and reduces dosing frequency, all of which contribute to better therapeutic outcomes.[6] Several GRDDS approaches have been reported, including floating systems, mucoadhesive systems, expandable systems, high-density systems, and super-porous hydrogels.[7][8] Among these, floating drug delivery systems have attracted particular attention due to their ability to remain buoyant in gastric fluids without affecting gastric motility.[9]

Within floating systems, micro-balloons (also known as hollow microspheres) are emerging as a highly versatile carrier for controlled oral delivery. Micro-balloons are spherical, porous, and low-density particles that float on gastric contents for extended durations.[10] Their hollow core, typically generated through techniques such as solvent evaporation, emulsion-based methods, or spray drying, provides excellent buoyancy and prolonged retention in the gastric region.[11] Micro-balloons exhibit several advantages, including improved bioavailability of poorly soluble drugs, reduced dosing frequency, controlled and sustained release, and minimized systemic side effects.[6] Furthermore, their fabrication allows for flexibility in size, porosity, and drug-loading efficiency, making them suitable for both synthetic and herbal drug incorporation.[12]

Parallel to advancements in novel carriers, interest in herbal medicines has been steadily increasing worldwide. Herbal formulations are widely recognized for their diverse pharmacological activities, relative safety, and cost-effectiveness compared to synthetic drugs.[13] They have been traditionally employed in the management of numerous chronic and infectious diseases, and their acceptance has grown due to the shift toward natural therapies.[14] However, herbal drugs often face similar limitations as synthetic drugs, such as poor solubility, instability in the gastrointestinal environment, and short residence time.[15] Encapsulation of herbal extracts into micro-balloons can effectively address these issues by shielding bioactive phytoconstituents from degradation and enabling sustained release in the gastric environment.[16]

Among various medicinal plants, Thuja occidentalis (commonly known as white cedar or arbor vitae) offers considerable potential in novel drug delivery applications. A member of the Cupressaceae family, Thuja is native to North America and widely cultivated across[17] Europe and Asia.[18]

It has long been used in traditional medicine systems such as Ayurveda, Unani, and homeopathy for the treatment of respiratory infections, skin diseases, rheumatism, and other ailments.[19] Phytochemical studies have demonstrated that Thuja contains a range of bioactive compounds, including volatile oils (α-thujone, β-thujone, fenchone), flavonoids, tannins, and diterpenes.[20] These constituents contribute to its pharmacological properties, such as antimicrobial, antioxidant, anticancer, antiviral, anti-inflammatory, and hepatoprotective activities.[21]

In this context, Thuja-loaded micro-balloons present an innovative strategy that bridges the gap between herbal medicine and advanced drug delivery systems. This approach aligns with the global trend of integrating natural remedies into contemporary pharmaceutical sciences while addressing the fundamental challenges associated with oral drug delivery. The present work aims to highlight the potential of gastro-retentive micro-balloons as a delivery platform for Thuja occidentalis, emphasizing their role in improving drug performance, patient compliance, and therapeutic outcomes.[22]



Figure 1: Thuja Leaves.

Species	Botanical origin	Geographical Distribution
Thuja occidentalis	Arborvitae, White cedar	North America & Europe
Thuja Koraiensis	Korean Thuja	North and South Korea, the Changbai Mountain area of China, adjacent regions of Sichuan province in China
Thuja plicata	Western Red Cedar	USA: Alaska, Montana, Washington, Oregon, California; Canada: British Columbia
Thuja standishii	Japanese Thuja	Japan
Thuja sutchuenensis	Sichuan Thuja	Northwestern China, Sichuan Province
Thuja orientalis	Oriental Thuja	China, Korea, Mongolia, and parts of Japan

2. Gastro-retentive Drug Delivery Systems (GRDDS)

In pharmacy, traditional oral delivery is most commonly used to cure diseases. One of the major drawbacks of traditional delivery is non-site specificity. There are some medications that can be absorbed only by a particular site. Such drugs need to be delivered at a particular site or in a manner that will deliver maximum medication to the site. These site-specific drugs are the focus of the pharmaceutical industry today. Gastro-retentive delivery is one of the delivery methods for a site-specific drug to the stomach or intestine. It is obtained by having the dosage form resident in the stomach and releasing the drug in a controlled manner to a specific site, i.e., duodenum, intestine, or stomach.[23] Gastro-retentive Drug Delivery Systems (GRDDS) were developed to solve this. The concept of GRDDS is to formulate dosage forms that can stay in the stomach for an extended period of time and deliver the drug through a controlled release.[24]

Drug delivery systems have been created in a way that the therapeutic index of drugs is maximized and side effects are minimized. Oral drug delivery is the most widely used route of drug delivery because of cost-effectiveness and convenience, which ensures patient compliance. More than 50% of drug delivery systems released are for oral routes. The oral

route is favored because it has the potential to be an incredibly efficient drug delivery system that can be controlled by a large variety of factors such as the process of gastric emptying, dosage form transit time through the gastrointestinal tract, release of drug from the dosage form, and absorption site for the drug. One of the advantageous features of oral route is that it provides a good level of compliance from the patient. Alteration of gastrointestinal transit time is one of the major problems in developing an oral controlled drug delivery system. Drug gastric emptying is very variable and depends on dosage form and fed or fasted stomach state. Typically, the average gastric holding time ranges from 5 minutes to 2 hours.

The gastrointestinal tract can be divided into three main categories

a) Stomach

b) Small intestine - duodenum, jejunum, and ileum

c) Large intestine

The gastrointestinal tract is a muscular tube measuring 9 meters from mouth to anus. Its main roles are to absorb nutrients and expel waste through the physiological functions of digestion, absorption, secretion, motility, and excretion. The stomach has three layers of muscles referred to as oblique muscles and is found in the proximal part of the stomach, running over the fundus and upper parts of the gastric body. The stomach is anatomically separated into the body, pylorus, and fundus.[25] The stomach is a shape organ located in the upper left-hand portion of the abdomen. The main function of the stomach is to store the food temporarily, grind it, and release it slowly into the duodenum.

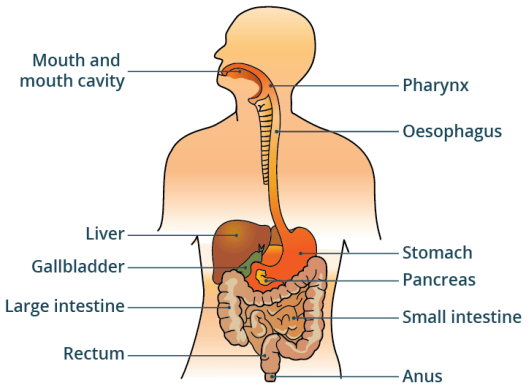


Figure 2: General Gastrointestinal Tract.

Stomach physiology

Anatomically, the stomach is subdivided into three parts: the fundus, body, and antrum (pylorus). The postprandial capacity of the stomach is about 1.5 liters, whereas during

interdigestive state, the volume of the stomach is 250 to 500 milliliters. It secretes around 2 liters of the total 8 liters of fluid contained in the gastrointestinal tract. The body and fundus act as a reservoir of food that has not been digested, whereas the antrum is used mainly for mixing and acts as a pump to promote gastric emptying through propulsive movements. The passage between the duodenum and stomach is the pylorus. Based on capacity, the pylorus has an important role in the residence time of gastro-retentive drug formulations (GRDF) in the stomach. Gastric emptying enables the bolus to leave the stomach and takes place during the fed and fasting states. The patterns of motility, however, are different under the two conditions; motility is stronger during fasting compared to when fasting. In fasting, there is a sequence of electrical events called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC) that cycles at every 2 to 3 hours by stomach and intestine. It is also further divided into four phases as below

- Phase I (basal phase) is of 40 to 60 minutes' duration and is marked by lack of frequent contractions.
- Phase II (pre-burst phase) similarly takes 40 to 60 minutes with interspersing action potentials and rising intensity and frequency of contractions as the phase continues.
- Phase III (burst phase) is 4 to 6 minutes long and characterized by robust and forceful contractions for a short duration.
- Phase III plays a role in pushing food that is not digested out of the stomach and into the small intestine and is also known as the housekeeper wave.
- Phase IV continues from 0 to 5 minutes and is a phase of gradually decreasing activity in preparation for the next cycle.[26]

Gastro-retentive Techniques

Several techniques, including floating, swelling, inflation, and adhesion, have been explored to increase the gastro-retention of dosage forms.[23]

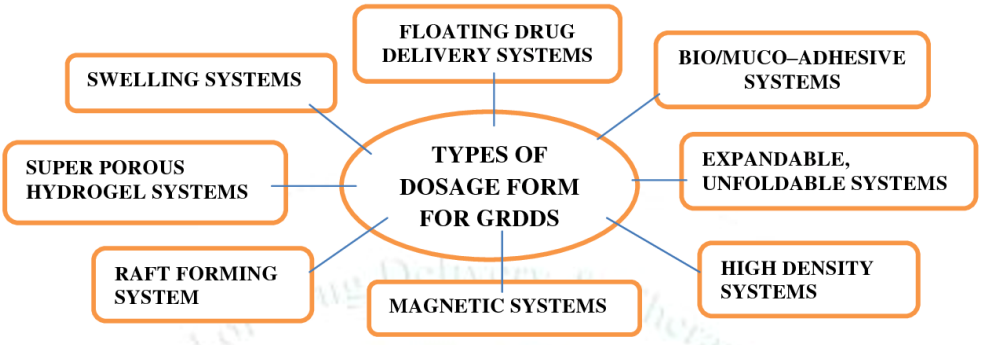


Figure 3: Gastro-retentive Techniques.

A) Floating systems

Floating systems possess a low density such that they float on gastric content and stay in the stomach for a considerable period. Under floating, the system dispenses the drug in a linear fashion at a constant rate, resulting in a longer gastric residence time (GRT) and reducing plasma drug concentration fluctuations.

B*) Bio/mucoadhesive systems*

Bio-adhesive drug delivery systems (BDDS) are a drug delivery device within the lumen to facilitate greater site-specific absorption of a drug. The approach utilizes bio-adhesive polymers that are capable of sticking to the surface of epithelial cells or mucin lining the stomach and extend GRT via greater closeness and contact time between the biological membrane and the dosage form.

C) Expandable, unfoldable, and swellable systems

For a dosage form to survive gastric transit, it should be larger than the size of the pyloric sphincter. However, it should also be very small to allow swallowing and should not cause gastric obstruction per se or on an aggregate basis.

D) High-density systems

High-density systems with a density of about 3 g/cm3 are housed within the rugae of the stomach and can withstand its peristaltic movement.

E) Magnetic Systems

This method of GRT augmentation is founded on the basic principle that the dosage form has a small inner magnet and an external magnet which is applied over the stomach area on the abdomen.

The Raft System utilizes alginate gels containing a carbonate component that interacts with gastric acid to form bubbles in the gel to enable it to float. Raft systems have been of considerable interest for use in drug delivery in gastrointestinal infection and disease.

G) Super Porous Hydrogels

They are swellable, but they are sufficiently distinct from other types to warrant a class of their own.

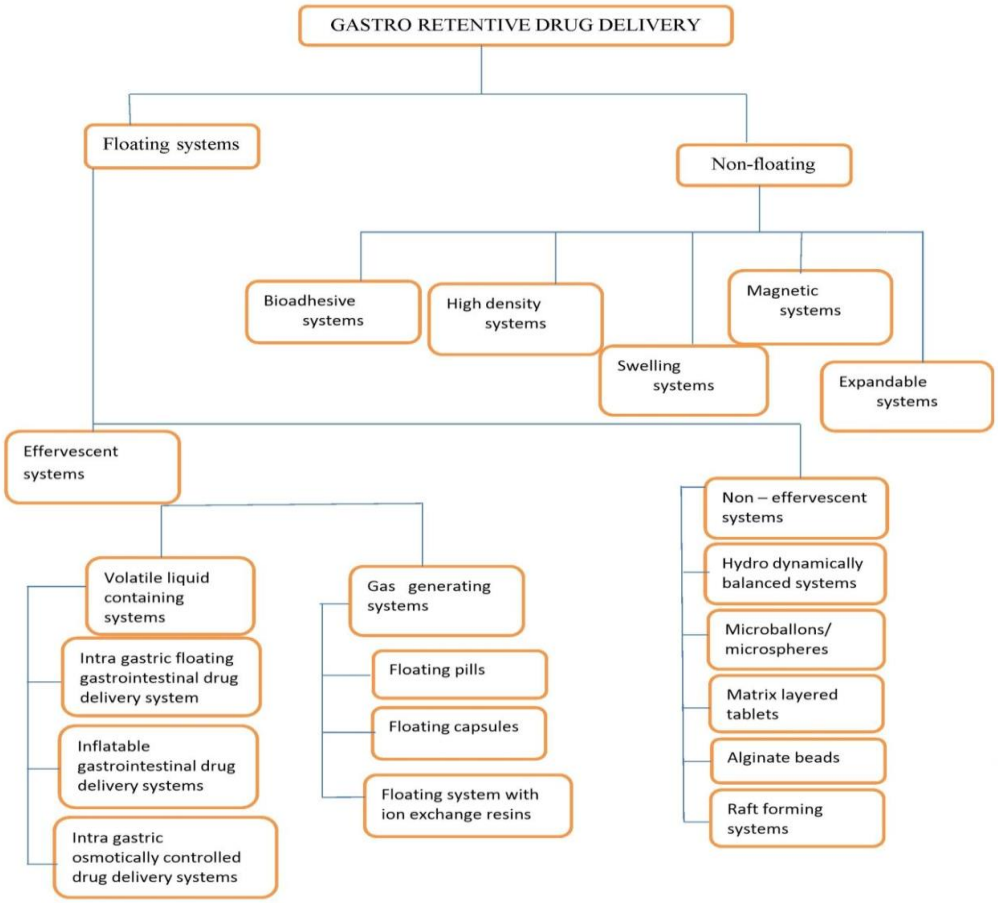


Figure 4: A flowchart illustrating various methods for gastro-retentive drug delivery.

3. Micro-balloons

Micro-balloons or microspheres are round particles without a central core. The hollow microspheres form a drug delivery system that also holds promise to be employed as an effective gastric retention method. Micro-balloons-based drug delivery systems consist of a non-effervescent mechanism of spherical particles with no central core, preferably kept less than 200 micrometers in diameter.[27] Micro-balloons are gastro-retentive drug delivery systems based on a non-effervescent approach. Micro-balloons in a strict sense are spherical, hollow particles. Micro-balloons are most often free-flowing powders of proteins or synthetic polymers.[28] Micro-balloons are low-density systems with sufficient buoyancy to float on top of gastric contents and maintain them in the stomach for a very prolonged length of time. The drug is released slowly in a controlled manner, resulting in higher gastric retention and less plasma drug concentration fluctuation. Micro-balloons improve compliance by shortening the dosing interval, thus providing an improved therapeutic effect for short half-life drugs.[29] Microspheres are solid spherical empty particles ranging in size from 1 to 1000 µm. Solid

biodegradable microspheres containing a drug dispersed or dissolved in the particle matrix hold the promise of controlled delivery of such a drug.[30]

Micro balloons make it possible for the release of a drug in a controlled manner at the target location. Micro balloons harboring a drug dispersed or dissolved in the particle matrix have the potential for controlled release of the drug. Some classes of drugs can benefit from the use of gastro-retentive devices. These include

• Locally acting stomach drugs
• Drugs that are mainly absorbed in the stomach
• Poorly soluble drugs at an alkaline pH
• Drugs with a narrow absorption window
• Drugs that are absorbed quickly from the gastrointestinal tract
• Drugs that degrade in the colon

Micro-balloons are gastro-retentive drug delivery systems using a non-effervescent system. Micro-balloons (Hollow microspheres) are, in a specific definition, empty spherical particles without a core. Microspheres are generally free-flowing powders consisting of proteins or synthetic polymers, best size less than 200 micrometers.[8]

Micro-balloons are considered to be one of the most beneficial buoyant systems because of their special advantages of multi-unit systems and improved floatability characteristics because of the central cavity space in the microsphere. Drug release at the required rate and floating properties are mainly controlled by the nature of the polymer, plasticizer, and solvents used in the preparation. Polymers like polylactic acid, hydroxy propyl methyl cellulose, and cellulose acetate are added to the formulation of hollow microspheres, and the regulation of drug release is possible by regulating the concentration of the polymer and the plasticizer-to-polymer ratio.[31]

Properties of Micro-balloons

• Micro-balloons typically have diameters between 10 and 200 µm, and their size distribution is an important factor in determining dispersion and overall performance of formulations.
• Micro-balloons are mostly spherical, and slight shape deviations (oval or irregular shapes) can influence packing, dispersion, and mechanical properties.

• With a hollow interior, the thickness of the wall in micro-balloons influences their attributes—greater wall thickness adds to their strength, while thinner walls result in less weight and greater insulation.

• Praized for being extremely light in weight, glass micro-balloons generally have densities ranging from 0.1 to 0.6 g/cm³, with polymer-based types weighing even less, thus making them ideal for light weight fillers.

• Polymer forms are lighter in weight and possess greater flexibility, while glass micro-balloons offer greater strength and insulation, and ceramic micro-balloons are more thermally and mechanically resistant and thus well suited to be used in high-temperature applications.

• Micro-balloons of larger surface area allow better interaction and bonding with matrix materials, and silane treatments of the surface can improve adhesion, compatibility, and dispersion in the composites.

• Glass micro-balloons have high compressive strength, whereas polymer types are more flexible and have lower stiffness (elastic modulus); their hollow structure enhances impact resistance by shock absorption in composite materials.[32]

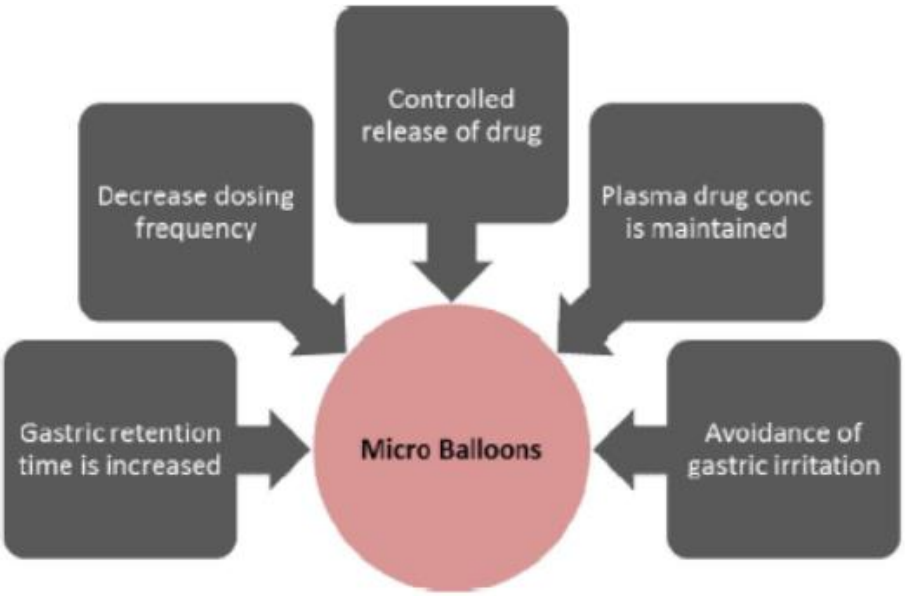


Figure 5

Micro-balloons have been widely accepted as a means to achieve oral release. The micro-balloons require a polymeric substance as a coat material or carrier.[1-3] Several different substances, both biodegradable as well as non-biodegradable, have been investigated for the preparation of micro particles. It is only reduces the dose of the drug, reaching the effective biological sites rapidly, but also results in reduced toxicity of the targeting.[33]

***Characterization of Micro-balloons*[29]**

Percentage Practical Yield

The prepared micro-balloons were collected and weighed. The measured weight was divided by the total amount of all non-volatile components, which were used for the preparation of micro-balloons.

$$\% \text{ Practical yield} = \frac{\text{Weight of dried micro-balloons}}{\text{Weight of solid used (excipients + drug)}} \times 100$$

Drug Entrapment Efficiency

Separation of free drug: Analysis of Telmisartan from micro-balloons was done by separating the free drug from the micro-balloon dispersion. The separation was done by filtration (Whatman filter paper) of micro-balloons. Then, the micro-balloons and filtrate were separated out.

Indirect method

In this method, analysis of the drug from micro-balloons was done by appropriately diluting the filtrate in distilled water, and absorbance was taken at 296 nm against distilled water as a blank on a UV-Visible Spectrophotometer. To find out % entrapment following equation was used.

$$\%EE = \frac{Weight\ of\ total\ drug - Weight\ of\ free\ drug\ in\ filtrate}{Weight\ of\ total\ drug}$$

Drug Loading Efficiency

% Drug loading was calculated using the following equation

$$\% \text{ Drug Loading efficiency} = \frac{\text{Weight of drug loaded in microballoons}}{\text{Total weight of powdered microballons}} \times 100$$

Buoyancy Study

Buoyancy is the force exerted by a fluid opposing the weight of a partially or fully immersed object.

$$\% \text{ Buoyancy} = \frac{Weight\ at\ time\ t}{Initial\ Weight} \times 100$$

Advantages

- Improves patient compliance by decreasing dosing frequency.

- Bioavailability is enhanced despite the first-pass effect because fluctuations in plasma drug concentration are avoided, and a desirable plasma drug concentration is maintained by continuous drug release.
- Gastric retention time is increased because of buoyancy.

Disadvantages

- Drugs having an irritant effect on gastric mucosa are not suitable candidates for FDDS.eg: NSAIDs, some antibiotics, digoxin, theophylline, corticosteroids, iron (ferrous sulfate), oral contraceptives, and tricyclic antidepressants.
- Drugs that are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable, e.g., nifedipine.
- They are not suitable candidates for drugs with stability or solubility problems in the stomach. eg. Ranolazine

4. Floating Drug Delivery System

Floating drug delivery systems (FDDS) have been designed to retain the drug in the stomach and are especially beneficial to drugs that are poorly soluble and have low stability in intestinal fluids. The basic idea behind FDDS is to develop a dosage form which is lighter in density than gastric fluids so that it floats on top. FDDS are hydrodynamically regulated systems that are light in weight and possess sufficient buoyancy to float over the gastric contents without affecting the rate of gastric emptying for a prolonged period. The rest of the system is washed out of the stomach as a part of the release of the drug, resulting in enhanced gastric residence time and better control over plasma drug concentration fluctuations. The principle of buoyant preparation gives a simple and efficient way to increase the gastric residence time of the dosage form with assurance of sustained drug release.[34]

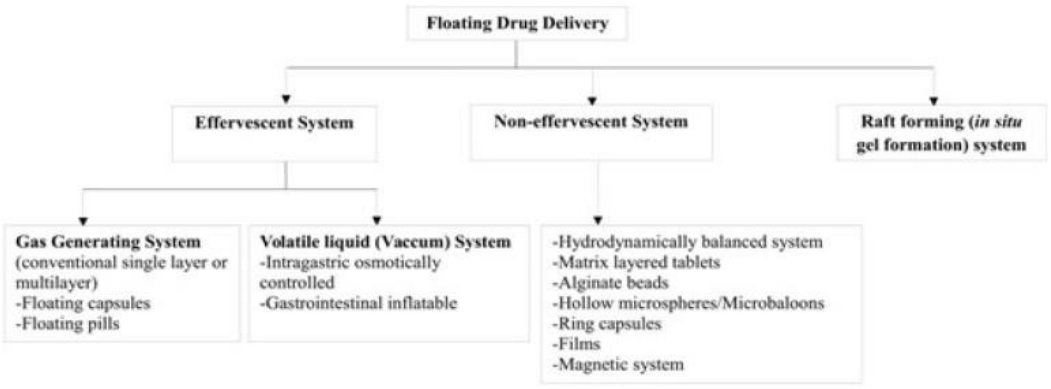


Figure 6: Classification of Floating Drug Delivery.

Floating drug delivery systems (FDDS) were created to maintain the drug in the stomach and are especially desirable for drugs that have poor solubility and low stability in intestinal fluids.

The basic idea of FDDS is to design a dosage form that is less dense than gastric fluids so that it can float on top.

FDDS are systems controlled hydrodynamically with low density and proper buoyancy, which allows them to float over the gastric contents without affecting the gastric emptying rate for a considerable time period.

The rest of the system is evacuated from the stomach along with the delivery of the drug, resulting in elevated gastric residence time and better control of plasma drug concentration fluctuations.

The principle of buoyant preparation gives a simple and efficient way to improve the gastric residence time of the dosage form with ensured sustained drug release.[35]

Mechanism of Floating Drug Delivery System

The system floats on the gastric contents the slow drug release has a required rate along with during the system flow on the gastric contents. The release is followed by removing the residual system from the stomach. However, with the desired level of floating force (F), levels of gastric contents are required to allow realization of the buoyancy retention principle and also to maintain the dosage form afloat on the surface of the meal. For determining floating force kinetics, a new device for determining resultant weight (RW) has been described in the literature. Its working involves determination of a force equal to F (in terms of time), which holds the object underwater. The object will float more effectively if RW is at the higher positive value. This device maximizes FDDS and negates its disadvantage, unpredictable intragastric buoyancy capability fluctuations, in terms of stability and longevity.

RW or F = F buoyancy – F gravity = (Df – Ds) gV

Where, F = total weight force, Df = density of the fluid, Ds = density of the object, V = volume, and g = acceleration due to gravity.[36]

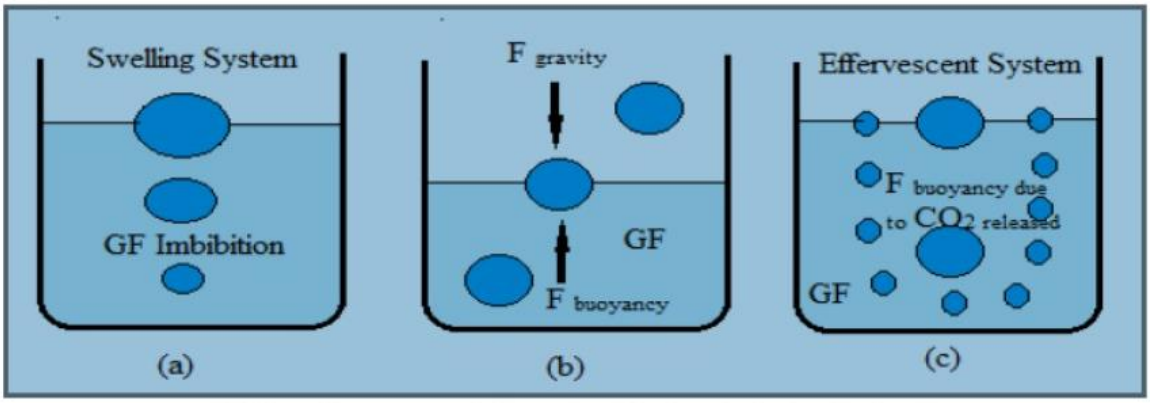


Figure 7: Mechanism of the Floating Drug Delivery System.

Application of the Floating Drug Delivery System

Enhanced Bioavailability

The bioavailability of riboflavin CR-GRDF is markedly improved when compared to the administration of non-GRDF CR polymeric formulations. Several processes related to the absorption and transit of the drug within the gastrointestinal tract operate simultaneously to affect the extent of drug absorption.

Sustained drug delivery

Oral CR formulations face challenges such as gastric residence time within the GIT. These challenges can be addressed with HBS systems, which can remain in the stomach for extended durations and possess a bulk density of less than 1, allowing them to float on gastric contents. These systems are relatively larger in size, preventing passage through the pyloric opening.

Site-specific drug delivery systems

These systems are especially beneficial for drugs that are absorbed specifically from the stomach or the proximal region of the small intestine. The controlled and gradual delivery of the drug to the stomach ensures adequate local therapeutic levels while minimizing systemic exposure to the drug. This approach reduces side effects associated with the drug in the bloodstream. Furthermore, the extended gastric availability provided by a site-directed delivery system may also decrease the frequency of dosing. For example, Furosemide and Riboflavin.

Absorption enhancement

Drugs that exhibit poor bioavailability due to site-specific absorption from the upper section of the GIT are ideal candidates for formulation as floating drug delivery systems, thereby

optimizing their absorption.

Less harmful effects in the colon

The trapping of the drug in the HBS systems of the stomach reduces the amount of the drug that reaches the colon. Thus, the undesirable effects of the drug in the colon can be prevented. Such a pharmacodynamic aspect justifies the rationale of the GRDF formulation of betalactam antibiotics, which are absorbed only in the small intestine, since their presence in the colon is among the reasons for the development of resistance in microorganisms.[37]

5. Thuja occidentalis

Thuja occidentalis, or the white cedar or Arborvitae, is native to the eastern parts of North America, including some parts of Canada and the northeastern United States. Its medicinal value was first recognized in an expedition in the 16th century when its use by indigenous people in Canada relieved weakness due to scurvy. Thuja occidentalis, in traditional medicine, has been applied to treat several ailments, including chronic inflammation of the bronchial tubes, urinary incontinence, low urinary tract infection, chronic inflammation of the skin, uterine cancer, amenorrhea, and rheumatism. Thuja, in current practice, is primarily utilized in homeopathy, as a mother tincture or in diluted form. Additionally, it is frequently used with other immunomodulating herbs like Echinacea purpurea, Echinacea pallida, and Baptisia tinctoria as part of evidence-based phytotherapy to treat both acute and chronic upper respiratory infections. It is also used as an adjunctive therapy with antibiotics for severe bacterial infections like bronchitis, angina, pharyngitis, otitis media, and sinusitis. While there have been many monographs and reviews of the botany, constituents, pharmacology, and uses of Thuja in the treatment of the common cold, such information is often outdated or in German only. As a result, we have attempted to present a contemporary, comprehensive, and evidence-based review of Thuja occidentalis, including its botanical characteristics, phytochemistry, in vitro and in vivo studies, safety, and efficacy.[38]

Kingdom	Plantae
Division	Coniferophyte
Class	Pinopsida
Order	Pinales
Family	Cupressaceae
Genus	Platycladus
Specific Epithet	Occidentalis
Botanical Name	**Thuja occidentalis**

General Characteristics

Thuja occidentalis, commonly known as Northern White Cedar, possesses several unique features

• **Appearance:** This evergreen species can reach heights of 30 to 50 feet and widths of 10 to 20 feet.

MATERIAL AND METHODS

Plant material

The leaves of T. occidentalis were gathered from the vicinity of Bhopal (M.P.) in February 2018. The specimen was identified by Dr. Zia-Ul-Hassan, a senior Botanist and head of the Botany department at Safia College of Arts and Science, Peer Gate, Bhopal. A herbarium of the plant was submitted to the specimen library of Safia College of Arts and Science, Peer Gate, Bhopal.

Chemical reagents

All chemicals utilized in this research were sourced from HiMedia Laboratories Pvt. Ltd. (Mumbai, India), Sigma Aldrich Chemical Co. (Milwaukee, WI, USA), SD Fine-Chem. Ltd. (Mumbai, India), and SRL Pvt. Ltd. (Mumbai, India). All chemicals employed in this study were of analytical grade.

Bacterial strain

The test organisms Pseudomonas aeruginosa (MTCC 2075), Bacillus subtilis (MTCC 1133), Salmonella (MTCC 1169), Bacillus cereus (MTCC 1305), Aspergillus niger (MTCC 872), and Candida krusei (MTCC 9215) were procured from the stocks of the Pinnacle Biomedical Research Institute, Bharat Scout & Guides Campus, Shyamla Hills, Bhopal, (M.P.).

Maintenance of bacterial culture

The bacterial strains were cultivated on nutrient agar media and incubated at 37°C for 24 hours, while the fungal strains were grown on SDA medium. Subsequently, the organisms were preserved on nutrient agar slants at a temperature of 4°C, and the purity of the cultures was routinely verified through plating.

General Characteristics

Thuja occidentalis, commonly referred to as Northern White Cedar, has several distinct characteristics:

• **Appearance:** This evergreen tree can grow between 30 to 50 feet tall and 10 to 20 feet wide.

MATERIAL AND METHODS

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Maintenance of bacterial culture

The Bacterial strains were grown on nutrient agar media and inoculated at 37°C for 24 hours, and the fungal strains were grown on SDA medium. Then organisms were maintained on nutrient agar slant at 4°C temperature and the purity of the organisms was checked at regular intervals by plating.

Plant material extraction

T. occidentalis leaves were collected, washed vigorously, and cleaned. The leaves were dried under a shaded environment and mechanically pulverized into a powder form. Around 500 g of the powder from the leaves was macerated using methanol and stored under ice-cold conditions for 72 hours to allow the extraction of phytochemicals. Following the three-day interval, the extract was passed through Whatman No. 1 filter paper to remove all un-

extractable materials such as cellular material and other insoluble components in the extraction solvent. The entire extract was concentrated to dryness in a rotary flash evaporator at reduced pressure and kept in a contamination-free, air-tight container for storage until needed. Finally, the percentage yields of the dried extracts.[39]

Pharmacological Characteristics

The main constituents of essential oils, mono- and sesquiterpenes, including carbohydrates, phenols, alcohols, ethers, aldehydes, and ketones, are responsible for the biological activity of aromatic and medicinal plants. Thuja orientalis is used internally in the treatment of coughs, haemorrhages, excessive menstruation, bronchitis, asthma, skin infections, mumps, bacterial dysentery, arthritic pains, and premature baldness. The leaves are antipyretic, astringent, diuretic, emmenagogue, emollient, expectorant, refrigerant, and stomachic. Their use is said to improve the growth of hair. The seed is aperient, lenitive, and sedative. It is used internally in the treatment of palpitations, insomnia, nervous disorders, and constipation in the elderly. The bark is used in the treatment of burns and scalds. The stems are used in the treatment of coughs, colds, dysentery, rheumatism, and parasitic skin diseases. Thujone was a weak inhibitor of acyl-CoA: lyso phosphatidyl choline acyltransferase activity in mouse brain synaptosomes compared to psychoactive cannabinoids.[40]

Inflammatory Activity

Vascular inflammation is involved in the inhibition and progression of cardiovascular disease, including atherosclerosis. Anti-vascular inflammatory activity of an aqueous extract of T. orientalis (ATO) and its possible mechanisms were investigated in human umbilical vein endothelial cells.[40]

Antifungal Activity

The essential oil showed antifungal activity in the inhibition zone against Alternaria alternata and Currularia lunata in a direct bioautography assay by the lipophilic leaf extract of T. orientalis. The best bioactive component (Rf = 0.80) was observed and noted for antifungal activity.[40]

Antibacterial Activity

Plants and their essential oils are potentially useful sources of antimicrobial compounds. Thuja orientalis contains large amounts of three substances (alpha, beta, and gamma thuja plicin) that, in low concentration, would serve as chelators for Salmonella typhimurium.[40]

Anti-Microbial Activity

The antimicrobial properties of Thuja occidentalis and other plant extracts have been investigated, revealing significant activities against various microorganisms.[38]

7. Critical Discussion

The given paper comprehensively discusses gastro-retentive drug delivery systems (GRDDS) and micro-balloons and their possible applications in oral drug delivery.

The paper mainly addresses the conjugation of these sophisticated systems with conventional medicine, namely, Thuja occidentalis. The paper, though, contains contradictions and issues that could be improved with the application of more stringent analysis. The paper cites Thuja occidentalis of the Cupressaceae family and in genus Platycladus. This seems to be a source of confusion in the paper given, where the specific epithet is written as Occidentalis. Though Thuja occidentalis is a common species under the genus Thuja, the table indicating the taxonomy of the plant incorrectly cites the genus as Platycaulus. This is a small but important inconsistency in a scientific abstract. The text further tells us that Thuja occidentalis occurs in North America, and is grown in Europe and Asia, whereas the table for species distribution indicates Thuja orientalis occurring in China, Korea, Mongolia, and Japan. This is followed by a sub-section of the pharmacological properties of Thuja orientalis, some of which are its applications against cough, hemorrhage, and skin infection, compared to the single focus on T. occidentalis in the entire introduction and subsequent sub-sections. Thuja occidentalis also goes by the name Northern White Cedar and is native to eastern North America, parts of Canada, and the north-eastern United States. It is described to be utilized by the original inhabitants of Canada for the cure of scurvy. The paper would have been improved with a more specific and clear focus on one species so that the reader is not confused. The paper affirms that Gastro-retentive Drug Delivery Systems (GRDDS), and also floating micro-balloons, bypass major issues associated with oral delivery of drugs, including low gastric residence time and inefficient drug absorption in the upper gastrointestinal tract.

The article informs that the low density of micro-balloons allows them to float on gastric content for extended periods of time, gradually and consistently releasing drugs.

It provides a single specific instance of the drug that was developed as micro-balloons (Telmisartan), but does not present any findings or data from the study. A stronger presentation would include some in vitro or in vivo data to support the allegations of

increased drug bioavailability and patient compliance. A thesis article refers to the advantages of concomitant use of herbal drugs with micro-balloons but lacks real examples or evidence for a Thuja-loaded micro-balloon system. The article states that Thuja has bioactive compounds such as α-thujone, β-thujone, flavonoids, and tannins with diverse pharmacological activities. But it does not spell out the particular problems involved in engineering these specific compounds into micro-balloons, i.e., stability or compatibility with the polymer to be used, and how the micro-balloon system would particularly address these problems.

The text here refers to general benefits, but a critical analysis would require a more concrete exposition of the utilitarian use.

8. Future Prospects

The article serves as the foundation for most of the prospective research and development strategies. Plant extracts and contemporary systems of drug delivery are converging rapidly. The future research would need to be focused on evolving standardized methods for the extraction and entrapment of some of the bioactive compounds of plants, such as Thuja occidentalis, into micro-balloons. This would involve the optimization of preparation techniques to improve drug loading and entrapment efficiency. Much research needs to be done to evaluate the in vivo behavior of these micro-balloons from herbs. This includes carrying out animal studies and, finally, human clinical trials to confirm the extended gastric retention, controlled release of drugs, and enhanced bioavailability. The article captures the significance of site-specific delivery of drugs absorbed in the upper GI tract, and future work might examine how Thuja-loaded micro-balloons might be constructed so that they would be delivered to a specific location for optimal absorption of their active ingredients.

Additionally, the paper also elaborates on various polymers utilized for the production of micro-balloons, like hydroxypropyl methylcellulose and polylactic acid. Future research can explore new biodegradable polymers with greater biocompatibility for herbal extracts and more efficient release kinetic control. Stability analysis should progress beyond mere practical yield and buoyancy to incorporate stability analysis in different pH conditions and mechanical stress to simulate the gastric environment accurately.

9. CONCLUSION

The provided text reviews the concept of herbal-based gastro-retentive floating micro-

balloons. It introduces the physiological challenges of oral drug delivery, the benefits of GRDDS, and the specific advantages of using micro-balloons as a delivery platform. The document also points out the rich pharmacological potential of Thuja occidentalis as a candidate for this system.

While the review outlines the theoretical framework well, it lacks specific experimental data to back its claims about Thuja-loaded micro-balloons. Future research is needed to connect theory to practical application by offering concrete results from in vivo and in vitro studies. This drug delivery system has a lot of promise. It could lead to better therapeutic outcomes, improved patient compliance, and more effective use of natural remedies. By addressing the need for more concrete evidence and standardizing the formulation processes, herbal-based micro-balloons could play an important role in modern pharmaceutical science.

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