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A COMPREHENSIVE REVIEW ON THE IRBESARTAN GASTRORETENTIVE FLOATING TABLETS

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Abstract : Irbesartan is an angiotensin II receptor blocker (ARB) commonly used for the treatment of hypertension. Its effectiveness mainly depends on two important factors — it belongs to the Biopharmaceutics Classification System (BCS) Class II category, meaning it has low solubility but high permeability, and it has a narrow absorption window in the upper part of the gastrointestinal (GI) tract. Because its biological half-life ranges between 11 and 15 hours, a sustained release formulation is needed to maintain 24-hour therapeutic action. Conventional tablets often move rapidly through the GI tract, which can lead to incomplete absorption and fluctuating plasma levels. To overcome this issue, gastroretentive drug delivery systems (GRDDS), particularly floating tablets, have been developed. These systems help the tablet remain in the stomach for a longer time, allowing a controlled and continuous release of the drug at its main absorption site. The review also discusses gastric physiology, such as the migrating motor complex, and explains the principles of flotation, both effervescent and non-effervescent. The importance of polymers like HPMC and Carbopol, along with solubility-enhancing techniques such as solid dispersions and cyclodextrin complexes, is also highlighted. Finally, it covers different characterization methods, including in vitro release kinetics and in vivo evaluation using gamma scintigraphy.

Index Terms - Irbesartan, Biopharmaceutics Classification, Gastroretentive Drug Delivery Systems, floating tablets

I. INTRODUCTION: -

Oral administration is considered the most convenient and favored method for delivering substances to systemic circulation. Recently, orally controlled release drug delivery has garnered significant attention in the pharmaceutical field due to its potential for enhanced therapeutic benefits, including ease of dosing, improved patient adherence, and formulation versatility. Drugs that are rapidly absorbed from the gastrointestinal tract (GIT) and have a short half-life are quickly cleared from systemic circulation. These types of drugs necessitate frequent dosing to maintain their therapeutic effect. To address these challenges, the development of oral sustained controlled release formulations aims to release the medication gradually into the gastrointestinal tract, thus sustaining effective drug levels in the systemic circulation over an extended period. Upon oral administration, such drug delivery systems are designed to remain in the stomach and release the drug in a regulated manner, ensuring a continuous supply to its absorption site within the gastrointestinal tract. Gastroretentive drug delivery represents a strategy aimed at extending gastric residence time, making it possible to achieve site-specific drug release in the upper gastrointestinal tract for both local and systemic effects. Gastroretentive dosage forms can exist in the gastric area for a longer duration, significantly extending the gastric retention time (GRT) of medications. Over the last several decades, various gastroretentive drug delivery strategies have been conceptualized and developed, including high-density (sinking) systems that stay in the stomach, mucoadhesive systems that adhere to the stomach lining, and unfoldable, extendable, or swellable systems that limit the passage of dosage forms through the pyloric sphincter [1]. Other systems, such as superporous hydrogels and magnetic systems, have also been explored. This review focuses on the various gastroretentive approaches that have emerged as prominent techniques in the realm of site-specific orally administered controlled release drug delivery systems [2,3]. The gastric emptying process of dosage forms is highly variable, and the capability to extend and regulate the emptying period is a valuable characteristic for formulations intended to remain in the stomach longer than traditional dosage forms. Several challenges arise in creating controlled delivery systems that ensure improved absorption and increased bioavailability [4].

Irbesartan, an angiotensin II receptor antagonist, is mainly prescribed for the treatment of hypertension. It is an orally active nonpeptide tetrazole derivative that specifically inhibits angiotensin II receptor type 1[5,6]. Angiotensin II receptor type 1 antagonists are widely employed to manage conditions such as hypertension, heart failure, myocardial infarction, and diabetic nephropathy. Irbesartan, classified as a drug with high permeability and low solubility, demonstrates slight solubility in alcohol and methylene chloride while being nearly insoluble in water. As a lipophilic drug, it possesses rapid oral absorption characteristics [6].

II. Drug profile: - [7]

Table No.01: Drug Profile of Irbesartan

Sr. No	Parameter	Description
a.	Generic Name	Irbesartan
b.	Chemical Name (IUPAC)	2-butyl-3-({4- [2-(2H-1,2,3,4- tetrazol-5-yl) phenyl] phenyl} methyl)-1,3- diazaspiro [4.4] non-1-en-4-one
c.	Molecular Formula	$C_{25}H_{28}N_6O$
d.	Molecular Weight	428.5 g/mol
e.	Category / Class	Angiotensin II Receptor Blocker (ARB) – Antihypertensive
f.	Appearance	White to off-white crystalline powder
g.	Solubility	It is soluble in alcohol and methylene chloride, and practically insoluble in water.
h.	pKa	4.24

1. Structure: -

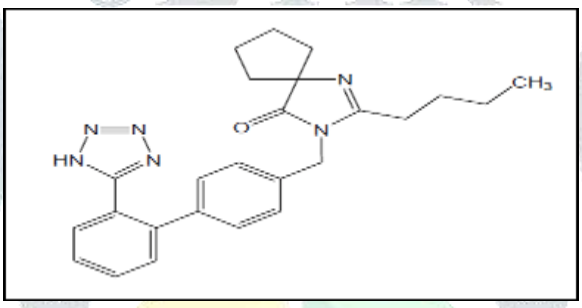

Fig No.01.: -Irbesartan [8]

2. Mechanism of Action: -

Irbesartan acts as a blocker of the angiotensin II type 1 receptor, classifying it as an angiotensin receptor blocker (ARB). In terms of how it works, irbesartan prevents the actions of angiotensin II, which is a strong vasoconstrictor formed from angiotensin I through a reaction facilitated by angiotensin-converting enzyme (ACE), also known as kinase II. As the main vasopressor in the renin-angiotensin system (RAS), angiotensin II prompts the adrenal cortex to generate and release aldosterone, increases cardiac contractility, promotes sodium reabsorption in the kidneys, heightens sympathetic nervous system activity, and encourages smooth muscle cell growth. Irbesartan mitigates the vasoconstrictive and aldosterone-releasing effects of angiotensin II by selectively attaching to the AT1 angiotensin II receptor. While there is also an AT2 receptor found in various tissues, it does not play a role in regulating cardiovascular balance [7].

3. Pharmacokinetic (ADME) Profile: - [9]

a) Absorption (A): Conventional oral formulations achieve a high average absolute bioavailability of 60-80% (following dissolution in the intestine). Peak plasma concentrations (Tmax) are typically attained within 1.5-2 hours post-administration.

b) Distribution (D): Irbesartan is extensively bound to plasma proteins (approximately 96%, primarily albumin).

c) Metabolism (M): Hepatic metabolism occurs predominantly through oxidation (mediated by the CYP2C9 enzyme) and glucuronide conjugation. Its resultant metabolites are largely pharmacologically inactive.

d) Excretion (E): Elimination proceeds via a dual pathway, encompassing both biliary and renal routes. Its prolonged terminal half-life ($t_{1/2}$) of 11-15 hours supports a once-daily dosing regimen.

III. Floating system: -

Floating tablets, often referred to as gastro-retentive drug delivery systems (GRDDS), are innovative formulations designed to prolong the duration that pharmaceuticals remain in the gastrointestinal tract, specifically within the stomach. This approach is particularly advantageous for drugs with a brief absorption window in the upper GI tract, those that require sustained action, or substances that are optimally absorbed in specific pH environments. Floating tablets employ various mechanisms to maintain their buoyancy in gastric fluids, enabling sustained release and enhanced bioavailability, therapeutic effectiveness, and may even facilitate a reduction in dosage

due to stable therapeutic drug levels [10].

1. **Classification of Floating Drug Delivery System: -**

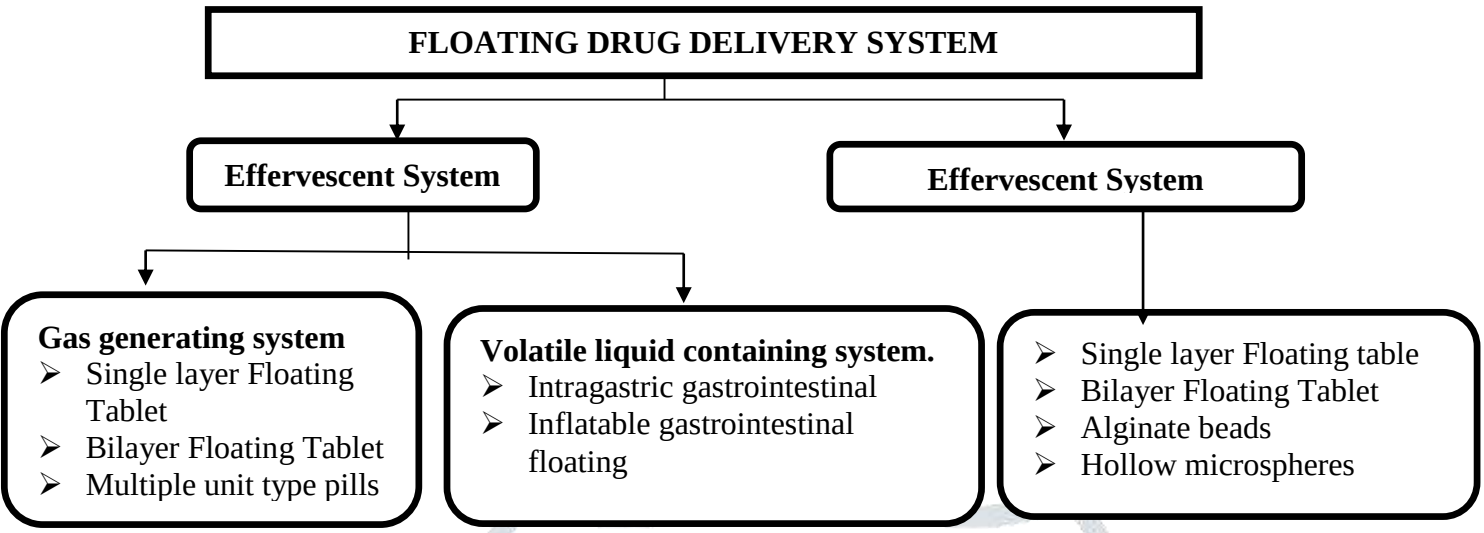

Figure 02: Schematic diagram classification of floating drug delivery system [11].

IV. Materials And Methods: -

1. **Materials: -**

Hydroxyproprylmethylcellulose, K4M, K15M, K100M. Microcrystalline cellulose, Lactose, sodium bicarbonate, magnesium sterate, and talc

2. **METHODS OF PREPARATION: -** [12]

Methodology for single-layer floating tablets: Essentially, single-layer floating tablets are produced using compression techniques. Typically, three primary compression methods are employed, which include:

- Direct compression,
- Dry granulation,
- Wet granulation.

A. Direct compression: The process of forming tablets directly from powdered substances without altering the physical nature of the materials is referred to as direct compression. This method is suitable for crystalline materials with favourable compressibility and flow properties, such as ammonium chloride, sodium chloride, methenamine, and potassium salts (including chloride, chlorate, and bromide). Single compression is utilized to create compressed tablets, where the upper and lower punches of the tablet machine apply significant pressure to the material once a specified amount of powdered tablet material fills a die.

B. Dry granulation method: This method involves creating granules by slugging when the tablet components are sensitive to moisture and/or cannot withstand high temperatures during drying.

C. Wet granulation method: In this approach, the active ingredient, along with diluents and disintegrants, is thoroughly mixed or blended in a rapid mixer granulator (RMG). The RMG is a versatile device that features an impeller and a chopper, designed for the high-speed mixing of dry powders with aqueous or solvent granulations. The moist materials from the wet milling phase are spread out on large trays and placed in drying chambers, where a circulating air current and a thermo-stable heat controller facilitate the drying process. Tray dryers and fluidized bed dryers are commonly used for this purpose. After drying, the granules are reduced in size by passing them through a finer mesh screen. Following this, a lubricant or glidant is incorporated in the form of a fine powder to enhance the flow of the granules. These granules are then compressed to form a tablet. Compared to wet granulation, dry granulation offers a more efficient and cost-effective manufacturing process, as it does not require heat or moisture, making it particularly appropriate for active ingredients that are sensitive to solvents or unstable under moist or high-temperature conditions.

3. **Excipients: -**

A. Gas-generating agents: - These organic acids are added to support sodium bicarbonate. They help regulate and sustain CO_2 production, ensuring fast floatation (low floating lag time) and stable buoyancy. Gas-generating agents are essential excipients in the formulation of floating drug delivery systems. They are responsible for producing carbon dioxide (CO_2) gas upon contact with gastric fluid, which gets entrapped in the polymer matrix, decreasing the tablet's density and allowing it to float on the gastric contents [13].

Ex. Sodium bicarbonate, citric acid, tartaric acid.

B. Diluents: - Diluents, also referred to as fillers, are inert substances incorporated into tablet formulations to enhance bulk, improve flowability, and ensure uniformity in weight and drug content [14].

Example. - Lactose, MCC, dicalcium phosphate.

C. Binders: - Binders are essential excipients that impart cohesiveness to the powdered material, ensuring that tablets remain intact after compression and maintain their mechanical strength during handling and storage.
Example. -PVP, starch paste.

D. Lubricants: -Lubricants form a thin layer between the tablet mass and die wall, reducing -Friction between particles, Adhesion to dies and punches, Facilitating smooth tablet ejection, Improving granulation flow. This ensures efficient tablet production.
Example. -Magnesium stearate, talc

E. Solubility Enhancers (for Irbesartan): Solubility enhancers are excipients used to improve the aqueous solubility and dissolution rate of poorly soluble drugs (BCS Class II), thereby enhancing their bioavailability. These agents work by modifying the drug's micro-environment, increasing wettability, forming micelles, or generating solid dispersions to keep drug molecules in a solubilized state [15].
Example: -Sodium Lauryl Sulfate (SLS), Poloxamer.

F. Coating materials: Coatings protect tablets from moisture degradation, masking unpleasant tastes. Making them easier to swallow.
Example. -Ethyl cellulose.

V. Conclusion: -

Gastroretentive floating drug delivery systems represent a promising approach for improving the therapeutic performance of drugs like Irbesartan, which have limited solubility and an absorption window in the upper gastrointestinal tract. By maintaining the dosage form in the stomach for an extended period and allowing sustained release, these systems enhance drug absorption, reduce dosing frequency, and improve patient compliance. The use of hydrophilic polymers such as HPMC and appropriate formulation techniques like wet granulation or direct compression ensures effective buoyancy and controlled drug release. The development of Irbesartan gastroretentive floating tablets thus offers a valuable strategy to overcome solubility-related challenges and achieve more consistent antihypertensive effects. Future research may focus on optimizing polymer combinations, improving in vivo performance, and scaling up for commercial production.

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