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Review Article

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A Review on Recent Research in Drug Targeting using Gastroretentive Drug Delivery Systems for Antihypertensive Drugs

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Abstract The preferred route of drug administration is via the oral route. Gastroretentive Drug Delivery Systems (GRDDSs) represent an innovative strategy within the pharmaceutical sector. Gastroretentive drug delivery systems (GRDDs) refer to dosage forms that are designed to remain in the stomach for an extended period of time. Gastroretentive drug delivery systems (GRDDSs) have the potential to improve the controlled release of drugs that have a specific absorption window by gradually administering the drug over an extended period until it reaches the intended site of absorption. The use of GRDDS is advantageous for drugs due to their ability to enhance bioavailability, therapeutic efficacy, and potential for dose reduction. Additionally, GRDDS can improve drug solubility, particularly for drugs that exhibit low solubility in high pH environments. This paper presents a discussion on the Gastroretentive Drug Delivery System of antihypertensive medication.

Keywords Gastroretentive Drug Delivery System, Floating, Antihypertensive, GRDDS, FDDS

Introduction

The utilization of drug delivery systems serves as a competitive strategy for expanding markets and indications, enhancing the longevity of products, and generating novel prospects [1-2]. According to literature, the preferred route of drug administration is through oral ingestion [3]. The oral route is widely preferred for systemic impact due to its convenient ingestion, painless administration, adaptability, and particularly, patient compliance. In addition, it has been noted that oral delivery systems with robust efficacy do not require aseptic conditions, thereby resulting in reduced production expenses [1-3]. Solid drug formulations are extensively utilized owing to their affordability, convenient administration, efficient dosage self-medication, pain mitigation, and particularly noteworthy, patient adherence. According to sources [3-4], tablets and capsules are the predominant solid dosage forms utilized. In various scenarios, a rapidly dissolving drug delivery mechanism is represented by a tablet that disintegrates or dissolves in the oral cavity without the requirement of water or mastication. In order to mask the flavor of the active ingredient, it is necessary for fast-dissolving delivery system films to incorporate certain substances [4-5]. Gastroretentive Drug Delivery Systems (GRDDSs) represent an innovative strategy within the pharmaceutical sector. Gastroretentive drug delivery systems (GRDDs) refer to dosage forms that are designed to remain in the stomach for an extended period of time. Gastroretentive drug delivery systems (GRDDSs) have the potential to improve the controlled release of drugs with a specific absorption window by gradually administering the drug over an extended period until it reaches the intended absorption site [6]. Gastroretentive dosage forms have the purpose of being retained in the gastric region for a prolonged duration, and subsequently releasing the drug candidates that have been inserted. This facilitates the continuous and extended input of drugs to the upper gastrointestinal tract, thereby ensuring the maintenance of optimal

bioavailability. This information is supported by reference 7. Consequently, these formulations not only prolong dosing intervals but also enhance patient adherence beyond the scope of presently accessible controlled release dosage forms [7-9]. The use of GRDDS is advantageous for drugs due to their ability to enhance bioavailability, therapeutic efficacy, and potential for dose reduction. Additionally, GRDDS can improve drug solubility, particularly for drugs that exhibit low solubility in high pH environments [10]. In addition to the aforementioned advantages, these devices offer pharmacokinetic benefits, including sustained maintenance of therapeutic levels over an extended duration, leading to a reduction in fluctuations of therapeutic levels. The preservation of gastric function could potentially yield advantages, such as facilitating the administration of products with limited absorption timeframes to the duodenum. Moreover, an extended duration of gastric retention within the stomach has the potential to confer advantageous outcomes for regional effects in the proximal portion of the small intestine [8-10].

Stomach's Physiology

The stomach performs the vital roles of food storage, mechanical breakdown, and initiation of preliminary stages of food digestion [11]. The stomach is an anatomical structure that possesses the capacity to retain and amalgamate ingested nutrients. Anatomically, the stomach is partitioned into three distinct regions, namely the fundus, body, and antrum (pylorus). Certain orders of mammals possess forestomachs that are highly sacculated, such as select artiodactyls and primates. The aforementioned partition is enduring in nature and serves to facilitate the process of food digestion [11]. The stomach, a heavily muscularized organ known as the duodenum, is situated between the esophagus and the initial segment of the small intestine. The upper portion of the stomach, known as the fundus, is situated in proximity to the diaphragm on the left side of the abdominal cavity. The pancreas is situated inferior to the stomach. The greater curvature envelops the greater omentum. The mucosal lining of the stomach comprises glandular structures that synthesize gastric secretions, primarily composed of main cells. This particular digestive secretion has the capacity to produce a volume of three quarts on a daily basis. The gastric glands are stimulated by parasympathetic signals from the vagus nerve, resulting in the secretion of gastric acid prior to the arrival of food in the stomach. This physiological process renders the stomach a reservoir for acid storage.

Distinct cells and functions are present in each region of the stomach. The stomach is divided into distinct sections, which are delineated as follows:

- The cardiac area is the anatomical location where the contents of the oesophagus are emptied into the stomach.
- The fundus is formed by the superior curvature of the organ.
- The primary central component of the organ is the body.
- The lower region of the organ, also referred to as the pylorus or atrium, facilitates the evacuation of the contents into the small intestine.

Two muscular valves, known as sphincters, ensure that the contents of the stomach remain contained within its confines.These are:

- The sphincter that separates the oesophagus and the heart.
- The pyloric sphincter, also known as the pyloric aperture, separates the stomach from the small intestine.

The stomach is supplied with nutrients by various branches including the hepatic left gastric, right gastric, and right gastroepiploic branches, in addition to the lineal left gastroepiploic and short gastric branches. The muscular coat is fed by them, after which they branch out in the submucous coat prior to their arrival at the mucous membrane. The arteries bifurcate into a network of diminutive capillaries at the bottom of the gastric tubules, which ascend amidst the tubules. The merging of capillaries results in the formation of a plexus that encompasses the tube apertures, ultimately giving rise to hexagonal meshes encircling the ducts. The veins emanate from these structures and traverse a linear trajectory downwards, intercalating between the tubules, until they reach the submucosal tissue, where they culminate in either the superior mesenteric vein or the portal vein in a direct manner. There exists a significant number of lymphatic vessels. The lymphatic vessels are comprised of two distinct layers, namely the superficial and deep layers, which follow the contours of the organ and lead to the lymph nodes. The nerves are distributed throughout various

sections of the organ, including the terminal branches of both the right and left urethras. The former are dispersed on the back, while the latter are located on the front. Additionally, a substantial quantity of sympathetic plexus branches originating from the celiac plexus are received by it. The nerve plexuses are situated within the submucosal and muscular layers of the gastrointestinal tract. The plexuses are responsible for providing fibrils to both the muscle tissue and the mucous membrane [11-13].

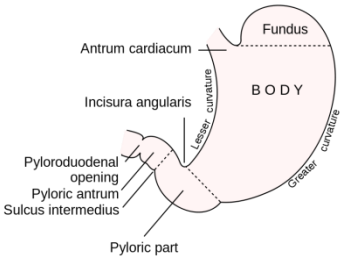

Figure 1: Diagram of Stocmach [11]

The desirable characteristics of a drug delivery system that can retain in the stomach for an extended period of time.

- Pharmaceutical agents exerting their effects specifically within the upper gastrointestinal tract.
- Pharmaceutical substances are primarily absorbed within the proximal portion of the gastrointestinal tract.
- At a basic pH, the solubility of drugs is reduced.
- Pharmaceuticals with a limited absorption range.
- Pharmaceutical substances are rapidly assimilated from the gastrointestinal tract.
- Drugs exhibit instability or degradation when exposed to a basic pH range of [5-10].

The prerequisites for Gastroretentive Drug Delivery System

- Pharmaceutical substances that are absorbed from the proximal segment of the gastrointestinal tract.
- Pharmaceutical substances that exhibit reduced solubility or susceptibility to degradation due to the alkaline pH environment present in the lower gastrointestinal tract.
- Pharmaceutical substances that exhibit absorption properties irrespective of the variability in gastric emptying time.
- Local or sustained medication administration to the stomach and proximal small intestine is a common therapeutic approach for certain medical conditions.
- This method is particularly effective in the treatment of peptic ulcers that are caused by H. Pylori infections. [8-11].

Approaches of Gastroretentive Drug Delivery System

The possible approaches of Gastroretentive Drug Delivery System are as follows:

- Low-density systems/ floating systems
- High density systems
- Expandable systems
- Bioadhesive systems
- Raft forming systems
- Bioadhesive systems
- Raft forming systems
- Super-porous hydrogel systems
- Magnetic systems
- Ion-exchange resin systems [14-25]

Gastroretentive drug delivery systems have many benefits like:

- • Greater availability in the body
- • Prolonged medication release
- • Localized delivery of medication
- • Less variation in plasma drug levels
- Selectivity of receptor activation has been enhanced. [7-9]

Gastroretentive drug delivery systems have many Limitations like:

The Gastroretentive Drug Delivery System can increase the bioavailability of drugs that have a small window of absorption. They do, however, have some limitations to their scope.

- GRDDS can't float and do their job unless there's a lot of fluid in the stomach.
- Drugs that cause ulcers are not an option.
- Colon-absorbable medications.
- Patients suffering from achlorhydria
- GRDDS are not appropriate for medications which are unstable and have solubility problems in stomach.
- Drugs that irritate the stomach lining should not be used for GRDDS.
- • First-pass-metabolized drugs like nifedipine are not good candidates. [25].

Gastric retention of dosage forms can be affected by a number of different factors.

- Gastric motility enhancers or depressants
- Fed or unfedstate- under fasting conditions
- Frequency of feed
- Caloric content
- Nature of meal
- Concomitant Intake of Drug
- Size
- Density
- Posture
- Age
- Gender
- Disease State
- Single or multiple unit formulation
- Shape of dosage forms

Floating drug delivery systems and their underlying mechanism

Along with the gradual release of the medicine, there is also an accompanying increase in the required rate during the system flow on the contents of the stomach.

Floating systems are divided into the following categories according to the buoyancy mechanism.

- Alginate beads
- Volatile Liquid/Vacuum Containing Systems
- Hollow microspheres
- Hydrodynamically balanced system
- Gas generating systems
- Microporous compartment systems
- Low density systems [17-26].

Evaluation of Gastroretentive Drug Delivery System

Pre compression parameters:

- Angle of repose
- Carr's compressibility index
- Hausner's ratio (HR)
- Tapped density
- Bulk density

Post Compression Parameters:

- Drug release study
- Drug content uniformity
- Friability test
- Hardness test
- Floatation studies
- Weight variation test [17-26]

Hypertension

"High blood pressure (hypertension) is a common condition in which the long-term force of the blood against your artery walls is high enough that it may eventually cause health problems, such as heart disease" [27].

Blood pressure is influenced by two factors: cardiac output, which is the amount of blood pumped by the heart, and peripheral vascular resistance, which is the amount of resistance to blood flow in the arteries. As blood pressure increases, cardiac output also increases while arterial diameter decreases. Blood pressure is typically expressed in millimeters of mercury (mm Hg). Both the systolic and diastolic blood pressures are crucial. Elevated values may indicate the presence of hypertension. Insufficient blood pressure levels, as evidenced by research [27-29], may result in compromised blood circulation to vital organs, including the brain.

Systolic Blood Pressure: The arterial blood pressure is a dynamic physiological parameter that continuously reflects the cardiac activity at any given moment, rather than remaining constant. During systole, the heart expels blood into the arteries. The forceful expulsion of blood into the arterial system results in an increase in arterial pressure. The systolic blood pressure is defined as the maximum pressure exerted by the blood against the arterial walls during cardiac contraction. According to established norms, an individual's systolic blood pressure while in a seated and relaxed state should not exceed 120 mmHg [27-29].

Diastolic Blood Pressure: The diastolic blood pressure refers to the arterial pressure during the resting phase of the cardiac cycle, specifically when the heart is not actively pumping blood into the arteries [27-29].

Sign and Symptoms: Hypertension is typically an asymptomatic condition. A significant proportion of individuals may remain asymptomatic. The manifestation of symptoms may require a prolonged period of time, possibly spanning several years or even decades, for the disease to advance to a discernible stage. However, it is possible that these symptoms may be attributed to an alternative cause. However, it is possible that these symptoms could be ascribed to alternative factors.

Manifestations of severe hypertension may comprise:

- chest pain
- shortness of breath
- headaches
- dizziness
- Pounding in your chest, neck, or ears
- Fatigue or confusion
- flushing
- nosebleeds
- blood in the urine
- visual changes [30-31]

Causes of Hypertension

There exist two distinct classifications of hypertension. Distinct etiologies are associated with each category.

Primary Hypertension

Essential hypertension, also known as primary hypertension, refers to high blood pressure that has no identifiable cause. This type of hypertension exhibits a gradual onset and lacks a clear etiological basis. This represents the most prevalent form of hypertension. The mechanisms underlying the gradual increase in blood pressure remain elusive to the scientific community. Several factors could be involved. Possible inclusions could encompass:

Environment: The adoption of unhealthy lifestyle behaviors, such as inadequate physical activity and poor dietary habits, can have a cumulative negative impact on one's physical well-being in the long run. Lifestyle choices have the potential to contribute to weight-related concerns. The likelihood of developing hypertension is higher in individuals who are overweight or obese.

Physical changes: The occurrence of any alterations within the body may lead to the manifestation of issues throughout the entirety of the organism. One potential concern that may arise is hypertension. Age-related alterations in renal function are known to disrupt the homeostatic regulation of sodium and water balance within the body. This shift may lead to an increase in your blood pressure.

Hypertension is a medical condition that exhibits a genetic predisposition in certain individuals. The possible cause of this phenomenon could be attributed to genetic abnormalities that are inherited or gene mutations that are passed down from one's progenitors [28-31].

Secondary Hypertension

Secondary hypertension has a more rapid onset and potentially greater severity compared to primary hypertension. Secondary hypertension may arise due to various factors, such as:

- thyroid problems
- adrenal gland problems
- obstructive sleep apnea
- congenital heart defects
- kidney disease
- side effects of medications
- alcohol abuse or chronic use
- certain endocrine tumors
- use of illegal drugs [28-31]

Table 1: Diagnosis of Hypertension [32-35]

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	120-129	80-84
High Normal	130-139	85-89
Grade 1 Hypertension	140-159	90-99
Grade 2 Hypertension	160-179	100-109
Hypertension Crisis	≥180	≥110

Pathophysiology of Hypertension

The etiology of essential hypertension is intricate and multifaceted. Hypertensive phenomena involve the intricate interplay of multiple organ systems and a multitude of independent or interdependent pathways. The kidney serves as both a contributing and a target organ in this regard. The etiology of hypertension is attributed to several crucial factors, including genetics, activation of neurohormonal systems such as the sympathetic nervous system and the renin-angiotensin-aldosterone system, obesity, and elevated dietary salt intake. Arterial hypertension (BP) is the medical term used to describe the state of having consistently elevated systemic blood pressure. Blood pressure (BP)

is determined by the multiplication of cardiac output and total peripheral vascular resistance, as stated in references [36-39].

Secondary hypertension constitutes approximately 5-10% of the total cases of hypertension, while primary hypertension accounts for the remaining cases. While the etiology of secondary hypertension is acknowledged, the underlying cause of primary hypertension, also known as idiopathic hypertension, remains unidentified. There are multiple etiologies that can lead to secondary hypertension. Irrespective of the underlying cause, an increase in arterial pressure can be attributed to an elevation in cardiac output, an elevation in systemic vascular resistance, or a combination of both factors. The two primary factors that lead to an elevation in cardiac output are heightened neurohumoral stimulation of the heart and augmented blood volume. The most common reasons for elevated systemic vascular resistance are heightened sympathetic activity or the impact of circulating vasoconstrictors. The optimal approach for managing secondary hypertension involves addressing or eradicating the root cause or pathology, while acknowledging that antihypertensive medications may still be necessary.

The following are enumerated as potential etiologies for secondary hypertension.

- Primary hyperaldosteronism
- Sleep apnea
- Renal artery stenosis
- Chronic renal disease
- Aortic coarctation
- Pheochromocytoma
- Preeclampsia
- Hyper- or hypothyroidism
- Stress [40-47]

Management of Hypertension

The hypertension can be managed by Lifestyle modifications and drugs. In lifestyle, it usually restricted by “dietary changes, physical exercise, weight loss, yoga, meditation etc.” [48-50].

“Several fitness regimes can be effective in lowering the blood pressure, including isometric resistance exercise, cardiovascular exercise, resistance exercise and breathing related exercise” [48-49].

Medications

Various antihypertensive drugs, such as calcium channel blockers, adrenergic receptor antagonists (beta and alpha blockers), vasodilators, aldosterone receptor antagonists, ACE inhibitors, renin inhibitors, diuretics, AT2 receptor antagonists, and endothelium receptor blockers, are currently available for the treatment of hypertension [51-53].

Some recent gastro-retentive drug delivery system of antihypertensive drugs are:

- Candesartan and Simvastatin gastro-retentive medication delivery system for the efficient control of hypertension [54].
- Gastro retentive drug delivery system intended for directing Losartan and Hydrochlorothiazide [55].
- Formulation, Optimization, and Evaluation of Gastroretentive Drug Delivery System of Nifedipine [56].
- Sucralfate and Metoprolol Succinate Bi-Layer Floating Tablet as Gastro Retentive Drug Delivery System [57].
- Development and Characterization of GRDDS of Hydrochlorothiazide [58].
- Azelnidipine, dihydropyridine based calcium channel blocker [59]
- Formulation and Evaluation of Propranolol HCl Floating Tablets [60]

Conclusion

The popularity of the Gastroretentive Drug Delivery System is expected to increase in the coming years owing to the availability of various innovations and a multitude of advantages.

Future Scope for GRDDS

The pharmaceutical industry has been primarily focused on controlling drug release profiles for antihypertensive drugs over the past 20 years. However, there is potential for the next two decades to shift the focus towards controlling gastrointestinal transit profiles. This shift could lead to the development of new products with unique therapeutic possibilities and substantial benefits for patients. In the near future, gastroretentive products that exhibit release and absorption kinetics lasting approximately 24 hours are poised to supplant conventional "once-a-day" formulations.

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