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An Evolving Approach to Gastro Retentive Drug Delivery System

[1]Daphne Sherine, [2]Sarath Kumar V, [3]Sathiyanathan R.
[1] *Associate Professor, P.S.V College Of Pharmaceutical Science & Research, Krishnagiri, India*
[2,3] *UG Student, P.S.V College Of Pharmaceutical Science & Research, Krishnagiri, India*
Corresponding Author: Daphne Sherine

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ABSTRACT
Inrecentyears,manyattemptshavebeenmadetoenhancethedrug'sbioavailability and therapeutic effectiveness of oral dosage forms. Gastric retention and controlled drug delivery are advantageous to many drugs having a low absorption window and poor bioavailability for that, various gastro retentive approaches are available like floating, mucoadhesion, swelling, multi-particulate systems, super porous hydrogel, etc. have been discussed. It is known that differences in gastric physiology factors such as gastric pH and motility exhibit both intra and inter-subject variability demonstrating a significant impact on gastric retention time and drug delivery behavior. English oral delivery drugs were most the commonly used modality because of patient compliance and ease of administration. Afteroral administrationofanydrug,itsbioavailabilityisaffected byitsresidencethetimeinstomach. This approach involves the development of a drug delivery system that can be delivered to the stomach. Some methods used to achieve gastric retention of drugs include the use of effervescence agents, mucoadhesive polymers and magnetic material. Our review article is in pursuit of giving detailed information about these methods and their designs, as well as factors that affect them.

Key words: Mucoadhesion, FDDS, Polymers, Porous hydrogel.

I. INTRODUCTION

Gastro retentive drug delivery is a newly discovered drug main approach of this delivery is to prolong the drug's gastric reside specific getting sits specific drug release in the upper GIT for local or systemic effects. Dosage forms formulated as gastroretentive drug system remain in the gastric region for prolonged periods[1], The useful system for GRDDS isa magnetic system, mucoadhesive system, bio-adhesive system, floating drug deliverydensity systemshigh-density system, drugexpendablesystemetc., thatsystemthosesystemistoincreasedrugbioavailability prolonged period in system[2].GRDDS are suitable for those drugs, which are absorbed fromthestomach(e.g.albuterol)[3]labileatalkalinepH (e.g.ranitidineandmetformin)[4] poorly soluble at alkaline pH (e.g. furosemide and diazepam)[5]and having a narrow window of absorption (e.g. riboflavin and levodopa) [6]. Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period,withoutaffectingthegastricemptyingrate[7].The hedevelopmentofgastroretentivedrug delivery systems (GRDDS) as a novel strategy for the controlled release of various medicines was pioneered[8,9]. Such systems can remain in the GIT for a prolonged time to deliver the active pharmaceutical ingredient (API) from its dosage form into the GIT.[10,11] Thesedevicescan release medications at the chosen pace and uptake region for a perpetuated length of time.[12]

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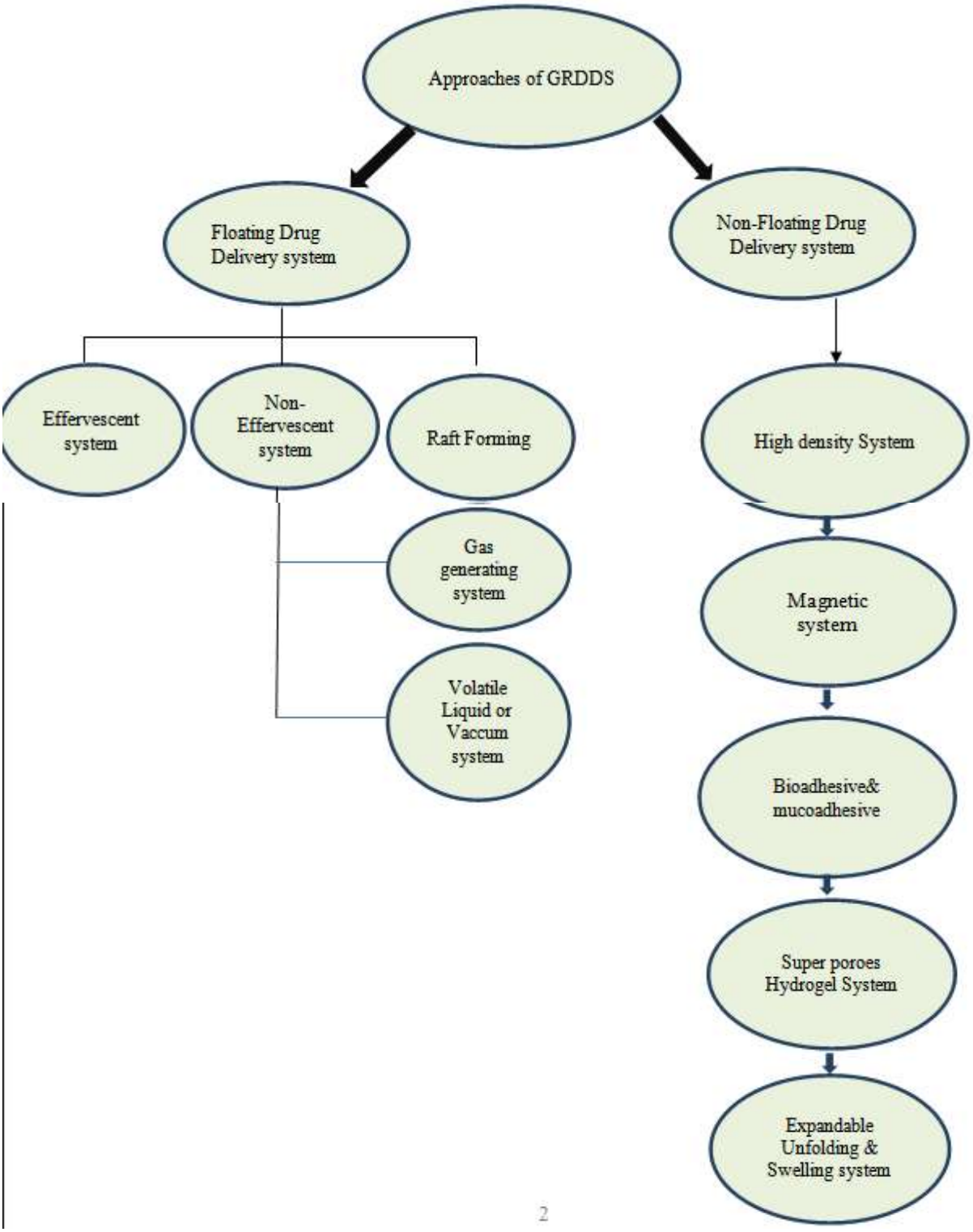
APPROACHES:



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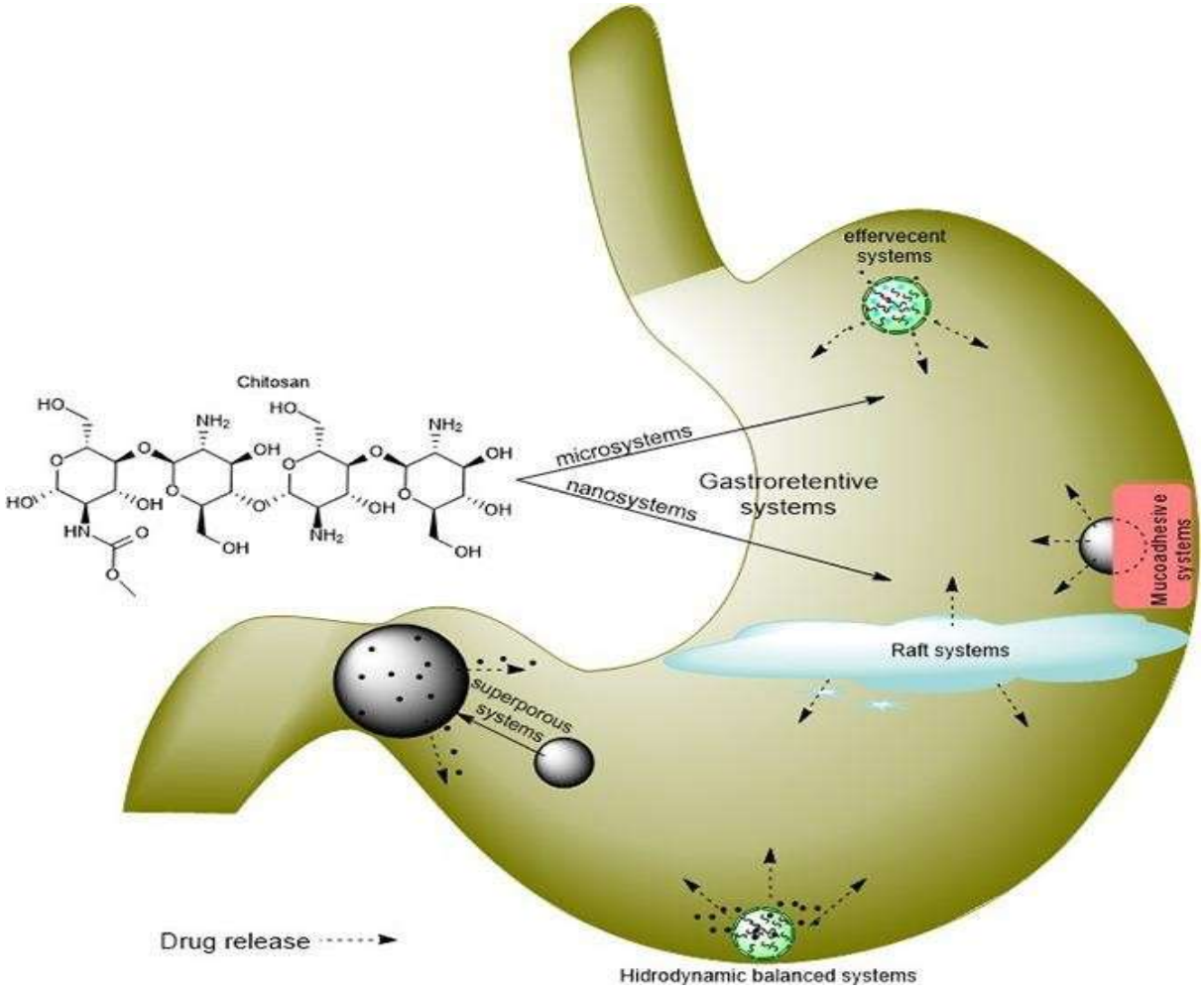
Floating Drug Delivery System [13]

Initially, the floating drug delivery system was introduced by sir Davis in the year 1968.Thesesystemsremainbuoyantduetolowerdensit yandprovidecontinuousdrugrelease. In this way, they increase the GRT of the drug and improve itsbioavailability.[14]



Properties for FDDS

- Slow drug release
- Act as a drugreservoir
- Bulk density should be lower than gastric fluid (Approximately 1.004 – 1.0gm/cm).
- Must form a cohesive gelbarrier

I. Effervescent

These types of systems are prepared by using swellable polymers, such as methylcellulose and chitosan, and effervescent compounds, such as sodium cyanate, tartaric acid, and citric acid. When they contact with acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids that provide buoyancy to the dosage form.[15]

II. Non-Effervescent

Non-effervescent dosage forms are formulated with a gel forming hydrocolloid, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. The drug is thoroughly mixed together with these ingredients before being administered. After oral administration this type of dosage form swells in contact with gastric fluids and attains a bulk density of <1.

III. Raft formingsystem

Here, a gel forming solution (e.g. Sodium alginate solution containing carbonates or

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bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to reduce gastricacidity. [16,17]

Non-Floating Drug Delivery System

I. High DensitySystem

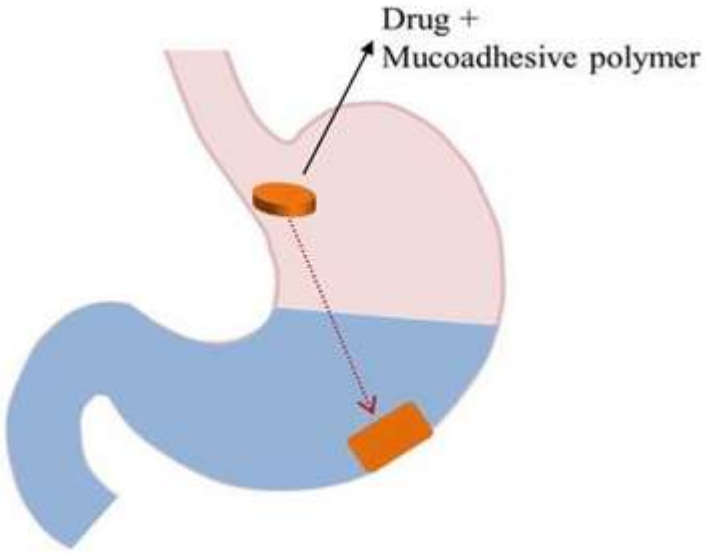
Whenhighdensitydosageform(capsule,Tablet,pellets)isgiventopatientbyoral route of administration the dosage form settles down at the bottom or sink in stomach, by entrapped in antrum and withstand the peristaltic wave of the stomach wall. In high density drugdeliverysystemformulationareformulatedbycoatinglayerofheavymetalorbymixing inertmaterialwithpharmaceuticalpreparation.Theinertmaterialincreasesthedensityupto1.5 – 2.4 gm/cm3, according to the density present in the stomach GI transit time of pellet can be extent from 6 – 24 hours (as they are small), its rate of dispersion decreases. The product of high-density system is not marketed because its ineffective in humans till, research and development are ben working on it.[18]

II. MagneticSystem

Inmagneticsystemapproaches,asmallmagnetisinsertedindosageformaswell as in abdomen over the position. The gastric residence time of dosage form can be enhanced by extra incorporated of magnet. Prolong absorption of drug is possible. Initially the technological experiment was performed on rabbit with bioadhesive granule containingultra- fine ferrite. Granule where transfer to esophagus with an external magnet of 1700 G for the initial 2 min and (interval of 2 min) almost all the granules were retained in the region after2 – 10 hrs.[19]

III. Bio-adhesive / Mucoadhesive System

To have a complete adhere in mucosal membrane some excipients are usedsuch as lectins, Carbopol, chitosan, gliding etc., those excipients help to increases absorption for prolong time in stomach as well as GI track. Thissystem is also based on target drug delivery, site specificdelivery.[19]



IV. Expandable unfolding and swellingsystem

In this drug delivery approaches the dosage size increases as dosage form reacted to gastric fluid. The size of dosage form (tablet, capsule, pellets) gets bigger than the pyloric sphincter. The swelling is due to presence of swelling expandable agent such as gel, cellulose, HPMC etc., are responsible for swelling through osmatic absorption of water or gastric fluid. Initially the dosage form should be in normal condition as the dosage form is ingestedthroughoralrouteofadministrationthereactionoccurinstomachthedosageformget swell and float on thesurface.[21]

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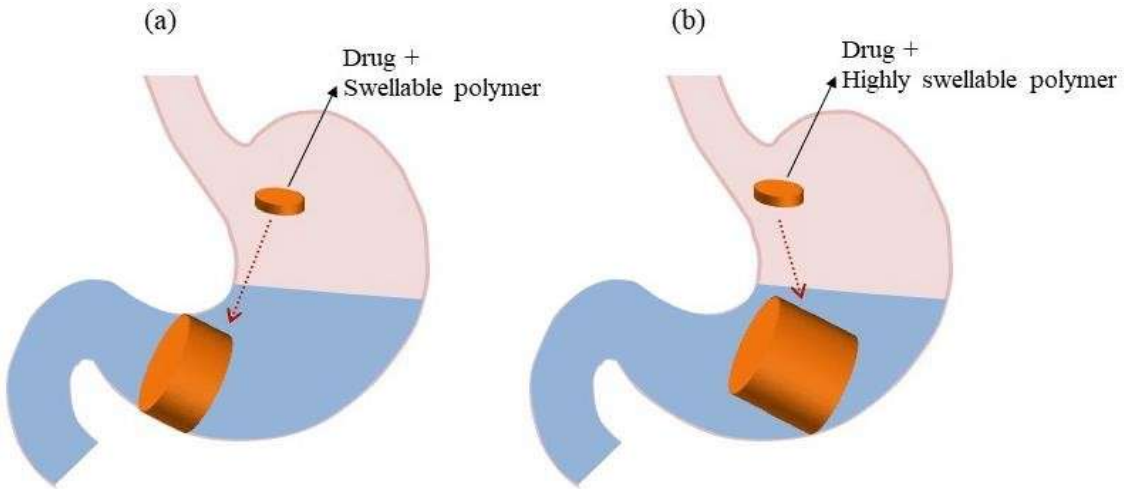

Following points are essential for the development of expendable system: -

- It should be in small (normal) dosage form for oralintake.
- Expanded Gastroretentiveform
- Should not cause gastricdestruction
- Finally, it should become small after releasing drug content fromsystem.[22]

Factors affecting the floating drug delivery system: [23,24,25,26,27]

1. Density:
The density of a dose form determines itsbuoyancy and, as a result, its floating efficiency. The dose form's density should be lower than the stomachic contents (1.004 gm/ml).

2. Shape of dosageform:
Tetrahedron and ring-shapeddevices have a higherfloating potential than other shapes. They have a 90-98 percent higher rate of 24-hour retention.20

3. Fed or unfed state:
GI motility is characterized by periods of robust motor activity, or migrating myoelectric complexes (MMC), which occur every 1.5 to 2 hours under abstinence settings.

4. Formulation of a single or multipleunit:
Multiple unit permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

5. Nature ofmeal:
Feeding indigestible polymers or fatty acid salts to the stomach can cause it to shift its motility pattern to a fed state, slowing gastric empty prolonging medication release.

6. Caloriecontent:
A high-protein, high-fat meal can extend floating time by 4–10 hours

7. Frequency offeed:
Because of the low frequency of migratory myoelectric complex, the GRT will increase by over 40 minutes when successive meals are providinginstead of a single meal (MMC).

8. Posture:
The GRT will differ between the patient's supine and upright ambulant stages. In the case of the floating systems, it was rumored that when individuals were kept in an upright ambulant position, the dosage type stayed consistent on stomachic content, as opposed to whenthey wereinasupineposition.Asaresult,thefloatingdrug deliverysysteminsidethe upright position of the patients is safeguarded against post-prandialevacuation

9. Age:
Elderly people, those over the age of 60, have a much longer floating time

10. Biologicalfactor:
Floating might vary depending on a person's health or physiological status. Diabetes and Crohn's illness, for example, affect floating time

11. Concomitant drugadministration:
Floating time is affected by anticholinergics like atropine, opiates like codeine, and prokinetic drugs like metoclopramide and cisapride.

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Evaluation of the Floating Drug Delivery System. [28,29,30,31,32,33,34,35]

1. Bulk density:

It's the proportion of a powder's total mass(m) to its bulk volume (Vo).

Db=m/Vo

2. Tapped density

It's the ratio of powder total mass (m) to powder tapped volume (Vi).

Dt = m/Vi

3. Compressibility index

The bulk density (o) and tapped density (t) of powder, as well as the rate at which it packs down, can be used to determine the flowability of powder. The compressibility index is obtained using

$$\frac{\rho t - \rho o}{\rho t} \times 100$$

Where,

ρo = Bulk density g/ml,

Pt = Tapped density g/ml.

4. Hausner's Ratio:

It is calculated by taking the Tapped density and dividing it by the Bulk density using the formula below

Hausner's Ratio = Tapped density / Bulk density

5. Angle of repose:

In this experiment, a funnel is filled within accurately weighed mixture of powder, granules, and microparticles. The funnel's tip can be adjusting such that just touches the apex of the blended heap. The mixtures can flow freely through the funnel on a horizontal surface. The diameter of the accelerated mass will be measured, and the angle of repose will be calculated using the equation below.

Tan θ = (h/r) θ= tan-1 (h/r)

Where,

θ = angle of repose

h = height of the heap

r = radius of the heap

6. Tablet dimensions:

A calibrated Venire Caliper was used to measure thickness and diameter.Three tablets of each formulation were chosen at random and measured separately for thickness.

7. Hardness:

Hardness indicates a tablet's capacity to with stand mechanical shocks while in use. A Monsanto hardness tester was used to assess the tablets' hardness. It was measured in kilograms per square meter. Three tablets were chosen at random and their hardness was determined.

8.Friabilitytest:

The Roche Friabilator was used to assess the friability of tablets. It was given as a percentage (percent). To begin with, ten tablets were weighed (W) and placed in the friabilator.Thefriabilatorwasspunat25rpmfor4minutes orturnedupto100timesthe tablets were weighed once again (Wo). A formula was used to compute the percent friability.

%F = 100 (1-Wo/W)

9.Table density:

For floating tablets, tablet density was as excellent criterion. When the tablet's density is substantiallylowerthanthatofgastricjuice,itcanfloat mosteffectively (1.04).Thedensity was calculated using the followingformula:

10.Weight variationexperiment:

To test for weight variation, ten pills were chosen at random from each batch and weighed individually. The United States Pharmacopoeia allows for some variation in tablet weight.

11.Determination of buoyancy lagtime:

The buoyancy lag is the time it takes for the tablet to rise to the surface and float. The buoyancy of pills was investigated in 900ml of artificial stomach fluid at 370.5^0C. The buoyancy lag time was measured with a stop watch, and the entire floating time was visually observed.

12.Floatingtime:

throughout the investigation, float time was monitored using a USP dissolving apparatus- II at 50rpm with 900ml of 0.1N HCl and a temperature of 370.5 visual observation is used to determine the length of time the tablet floats within the dissolution media (including floating lag time, which is the time it takes for the tablet to rise to the surface).

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13.Swellingindex:
The floating sustained release layer tablets were subjected to a swelling test. The tablets were placed in a USP dissolution apparatus II containing 900ml of 0.1N HCl and allowed to expand to a constant weight while being kept at 372^0C. The tablets were removed, wiped with filter paper, and the weight changes were calculated. The experiments were carried out three times. The method was then used to calculate the degree of swelling (the swelling index).

$$\text{Swelling index} = \frac{Wg - Wo}{Wo} \times 100$$

Where,
W_o is the initial weight of tablet.
W_g is the weight of tablet at equilibrium swelling in the medium.

14.Drugcontent:
Five tablets from a batch were picked at random, weighed, and ground in a mortar. In a standard flask, a properly weighed quantity of powdered tablet equivalent to 100 mg was placedandfilledtothemarkwith0.1NHCL;thesolution wasthenfiltered througha0.45 um membrane paper. The spectrophotometric method was used to conduct theanalysis.

15.Surface topography:
The surface topography and structures were determined using a scanning electron microscope (SEM, JEOL JSM–6701F, Japan) with a 10 k.v acceleration voltage, acontact angle meter, atomic force microscopy (AFM), and a contact profilometer (Ichikawam et al.,1991).

Advantages of GRDDS. [36,37]
- ✓ Improvesthebioavailabilityofdrugandwhichism etabolizedintheupperpartoftheGIT.
- ✓ Reduces dosing frequency for the drug with a relative short duration half – life, thereby, improving patient'scompliances
- ✓ Prolong and sustained release of drug facilitates local therapeutic response in the upper smallintestineastomach.Enhancedabsorptionof drugswhichsolubilizeonlyinstomach.
- ✓ Drug releases in controlled manner for prolongedperiod.
- ✓ Site-specific drug delivery to stomach can beachieved.

Disadvantages of GRDDS. [38,39]
- ✓ The swelling formulation can be swelled in the system before reaching the site of the stomach
- ✓ Longer time required to swell for hydrogel based swellingsystem.
- ✓ The Mucoadhesive dosage contains several limitations regarding the increase rate of the mucus layer, solubility factor, and thickness of the mucuslayer.
- ✓ Before achieving the stomach site, the swellable formulations can swell in thesystem.
- ✓ It offers lag gastric emptying time(GET).

APPLICATIONS.[40]
- ✓ **Reduced undesirable activity at thecolon**:

The drug maintenance in the hydro dynamically balanced system (HBS) is affected by the present drug in the intestine and also their action is restricted.
- ✓ **EnhancedBioavailability:**

The drug riboflavin bioavailability is enhanced by Control Release Gastro retention delivery formulation (CRGRDF) Other than non-GRDF CR dosage forms.
- ✓ **Absorptionenhancement:**

Forthedevelopmentofafloatingsystemsomedrugshav epoorbioavailabilityatthetargetsite of GIT and regulate absorption.
- ✓ **Site-specific drug deliverysystems:**

Thesite-specificdrugconveyanceframeworks implythatthemedicationsarecaughtupinthe small digestive tract and the stomach site. For the controlled way of the medication at the site of the stomach shows better therapeuticsimpacts.

II. CONCLUSION:

In this paper, we have concluded that gastroretentive drug delivery systems are a great mode to treat gastrointestinal disorders. Because they provide local action in the stomach and produce long-term effects. In current reality, it is quite challenging to design effective dosage forms for gastrointestinal disorders. As a result, dosing is less frequent and the treatment is more effective. It is clear from the wide range of industrial products and patents issued in this industry that gastroretentive drug delivery systems are effective for treating digestive disorders.

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