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Formulation and Evaluation of Floating Drug Delivery System of Diltiazem Tablet

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Abstract: *The design and assessment of monolithic gastroretentive diltiazem dosage form s are described in the current study. As rate controlling polymers, hydrophilic cellulose derivatives, sodium alginate, sodium carboxy methyl cellulose, Polyox, and Methocel K100M in conjunction with Methocel E6LV are employed. Sodium bicarbonate was added as a gas producing substance.Wet granulation was used to make the tablets, which were t hen assessed for various characteristics, including thickness, diameter, homogeneity of drug content, friability, floating lag time, in-vitro buoyancy, in-vitro drug release studies, and stability studies. The results for every evaluation parameter were noteworthy. The medication and excipients did not interact, accor ding to DSC testing. It was discovered that the content of polymers and floating agents controlled the release rate, extent, and processes. The drug release kinetic s from the tablet were based on the Higuchi and Korsmeyer equations. In accordance with ICH rules, Formula F5 and F6 were both stored for three months at 40 °C/75% RH. Based on the findings of the research, F6 was determined to be the most optimal formulation out of all of the others. Formula F6 loaded with barium sulfate had a mean stomach retention duration of 5.50 ± 0.55 hours, according t o abdominal Xray imaging in eight healthy adult volunteers. It has been determined that the floating mechanism can be used to create the gastroretentive tablet of diltiazem HCI, extending its residence period and, consequently, its availability for absorption from the upper gastrointestinal tract (GIT) or stomach.*

Keywords: Floating drug delivery systems, multiple unit, bioavailability, gastric residence time

I. INTRODUCTION

Floating drug delivery systems (FDDS) have been developed to retain medication in the stomach, making them suitable for drugs with poor solubility and low stability in intestinal fluids. The concept behind FDDS involves creating dosage forms that are less dense than gastric fluids, allowing them to float on top. These hydro-dynamically controlled low-density systems possess enough buoyancy to float over the gastric contents and remain buoyant in the stomach for an extended period without affecting the gastric emptying rate.

Once the drug is released, the residual system is emptied from the stomach, resulting in prolonged gastric residence time and better control over plasma drug concentration fluctuations. This buoyant preparation principle provides a straightforward and practical way to increase gastric residence time for the dosage form and achieve sustained drug release[1]. Prolonging the gastric retention of a delivery system is beneficial for enhancing the therapeutic efficacy of the drug under specific circumstances. For instance, drugs that are better absorbed in the upper part of the gastrointestinal tract, as well as those with low solubility that degrade in alkaline pH, have been found to benefit from prolonged gastric retention. Additionally, for treating certain ulcerative conditions by providing sustained drug delivery to the stomach and proximal small intestine, prolonging gastric retention of the therapeutic moiety offers various advantages, including improved bioavailability and therapeutic efficacy with reduced dosing frequency [2]. provides a classification of FDDS, taking into account its physiochemical behavior and appearance. The retention of dosage forms in the stomach can be achieved using various methods, including floatation, mucoadhesion, swellable system, hydrodynamically balanced system, sedimentation, and expansion modified shape systems, among others (Streubel,

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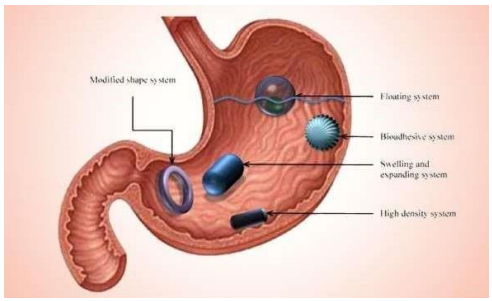
Siepmann, Bodmeier, 2006)[3]. Among these techniques, floatation is considered the most convenient and effective for gastric retention.

Gastroretentive floating drug delivery systems (GRFDDS) can float in the gastric medium for an extended period due to their lower bulk density compared to the gastric medium. This allows for constant release of the drug at a desired rate, enhancing the gastric retention time (GRT). The increased GRT leads to greater drug release in the gastric region, improving drug bioavailability and providing better control over fluctuations in plasma drug concentrations (Mayavanshi, Gajjar, 2008).[4] In this study, propranolol HCl (PPH) was chosen as a representative drug for creating gastroretentive floating drug delivery systems. PPH, classified as a beta-blocker, is utilized to manage high blood pressure, angina pectoris, irregular heart rhythms, prevent migraine headaches, hereditary tremors, hypertrophic subaortic stenosis, and tumors of the adrenal gland (Tripathi, 2003).[5] The peak concentration (Cmax) of PPH is reached 1 to 4 hours after oral administration, and its elimination half-life is 3-4 hours.

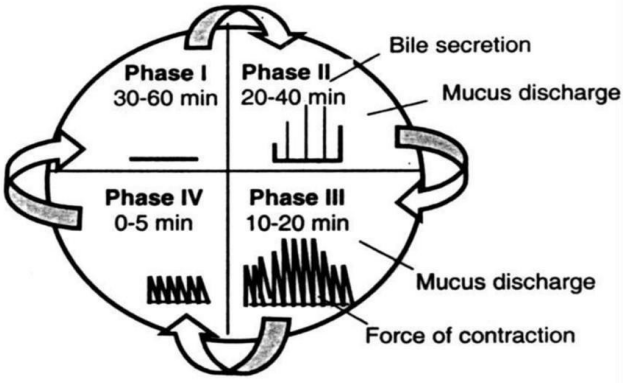
Due to its short half-life, conventional tablets need to be taken multiple times for optimal effect, or controlled drug delivery can be an alternative. Because of its brief half-life and insolubility in intestinal fluids (acid soluble basic drug), PPH has been identified as a suitable candidate for developing a gastroretentive dosage form (Srikanth et al., 2011b).[6]

Basic Gastrointestinal-Tract Physiology Stomach

- Fundas
- Body
- Pylorus or Antrum



MIGRATING MYLOELECTRIC CYCLE



APPROACHES FOR PROLONGING THE GASTRIC RESIDENCE TIME

1. HIGH-DENSITY SYSTEMS (HDS)
2. FLOATING SYSTEMS. (FS)
3. SWELLING AND EXPANDING SYSTEMS. (SS)
4. MUCOADHESIVE & BIOADHESIVE SYSTEMS. (AS)

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IMPORTANCE OF FDDS

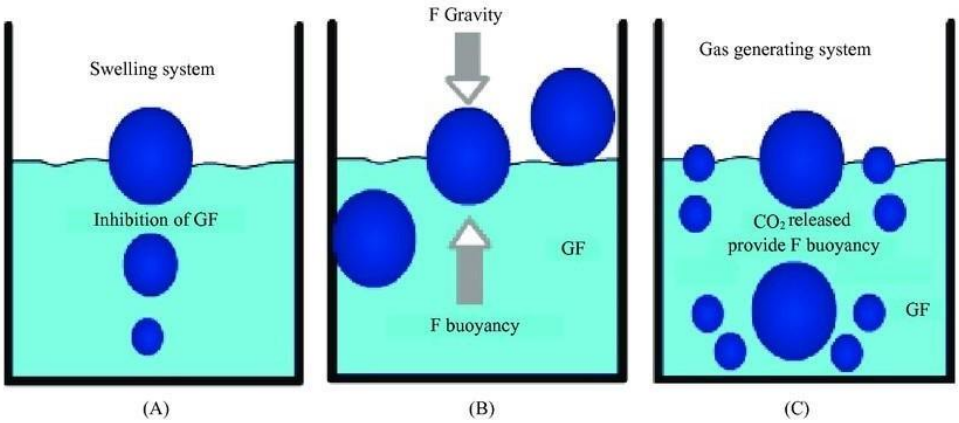
1. The gastric emptying time in humans which normally averages 2-3 hours through the major absorption zone (stomach and upper part of intestine) can result in incomplete drug release from the drug delivery system leading to reduced efficacy of administered dose.
2. Lower dosing and less side effects
3. Beneficial in the treatment of gastric diseases.
4. Suitable dosage forms for the drugs those are primarily absorbed in the stomach

MECHANISM OF FLOATING SYSTEM

FDDS has a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

F= F buoyancy - F gravity = (Df - Ds) gv

Where, F= total vertical force, Df= fluid density, Ds= object density, v= volume and g=. acceleration due to gravity.



FACTOR AFFECTING FLOATING TIME

- Density, size and shape of dosage form.
- Single and multiple unit formulation.
- Fed and unfed stage.
- Frequency of feed.
- Nature of meal.
- Age and gender
- Posture
- Biological factors

ADVANTAGES OF FDDS

- Enhanced bioavailability
- Sustained drug delivery/reduced frequency of dosing
- Targeted therapy for local ailments in the upper GIT
- Reduced fluctuations of drug concentration
- Improved selectivity in receptor activation

DISADVANTAGES OF FDDS

- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.

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- Not suitable for drugs that have solubility or stability problem in GIT.

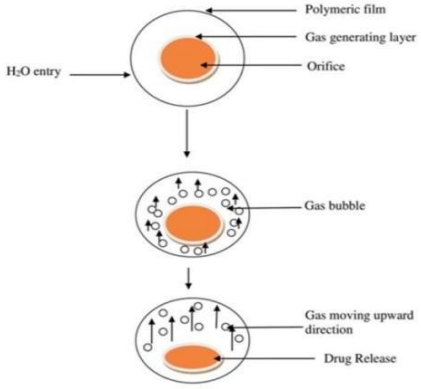
CLASSIFICATION OF FDDS

Effervescent system floating drug delivery system

The drug delivery system is composed of a matrix type and a swellable polymer, such as methylcellulose and chitosan, along with effervescent compounds like sodium bicarbonate, tartaric acid, and citric acid. This specific formulation allows for the liberation of CO2 and its entrapment in the swollen hydrocolloid upon contact with gastric juice, providing buoyancy for the dosage form. The delivery system is based on the design of a swellable asymmetric triple-layer tablet approach.[10-11]

Gas generating systems

The low-density FDDS relies on the release of CO2 when it comes into contact with gastric fluids following oral intake. The components are designed so that when they enter the stomach, CO2 is produced through a reaction with the acidic gastric contents, which then becomes trapped in the gel-based hydrocolloid (Fig 2). This creates an upward movement of the dosage form, keeping it buoyant and leading to a
reduction in the specific gravity of the dosage form, allowing it to float in the stomach. The CO2generating components are combined within the tablet matrix in either a single-layer or multi- layered form to create a gas-generating mechanism in the hydrocolloid layer, while the drug in the other layer results in a sustained release effect [13-14].



Volatile liquid containing systems

(Osmotically controlled drug delivery system) The system functions through osmotic control and involves a collapsible hollow unit with a deformable structure. This unit is attached to a housing divided into two chambers by a pressure sensitive movable unit. The first chamber typically holds an active drug, while the second chamber contains a volatile liquid that vaporizes at body temperature, causing the drug reservoir to float. To aid in the expulsion of the unit from the stomach, a bioerodible plug allows the vapor to escape [12-13].

Non-effervescent FDDS

The Non-Effervescent Floating Drug Delivery Systems are composed of gelforming or swellable cellulose hydrocolloids made of polysaccharides, as well as matrix-forming polymers such as polycarbonate, polymethacrylate, and polystyrene. The standard formulation process includes mixing the drug with gel-forming hydrocolloids that expand upon contact with gastric fluid after oral administration, maintaining the shape and density of the dosage form by trapping air within the swollen polymer, providing buoyancy [1415].

Colloidal gel barrier systems (Hydrodynamic balanced systems) The system is designed to increase the amount of drug that is absorbed in the solution form by prolonging the time it remains in the stomach. It achieves this by incorporating drug with gel-forming hydrocolloids, allowing it to float on the stomach contents. This system includes gel-forming cellulose type hydrocolloids such as hydroxypropylmethyl cellulose (HPMC), polysaccharides, and matrix forming

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polymers like polycarbophil, polystyrene, and polyacrylate. When the system comes into contact with gastrointestinal (GI) fluid, the hydrocolloid hydrates and forms a gel barrier around it. [16-17]

Microporous compartment systems

This innovation consolidates the epitome method of a sedate store interior a microporous compartment along side pores at best and foot dividers. The fringe divider of the medicate supply compartment is totally fixed to anticipate any direct contact of the gastric surface with the undissolved sedate. Within the stomach, the floatation chamber composed of captured discuss causes the conveyance framework to drift over the gastric substance. Gastric liquid enters through the gap, to the degree that it avoids theirsexist from the medicate and carrier the broken down sedate for nonstop transport over the digestive tract for absorption[18].

Floating Microspheres/Micro balloons

Praise microspheres moreover are known as small scale inflatables are considered as a most effective buoyant framework. It is composed of central honor space interior the microsphere. Honor microsphere is stacked with a medicate in their external polymer rack are manufactured by a novel dissolvable Dissemination strategy for emulsion [19].

Alginate beads/Floating beads

Multi-unit coasting dose shapes have been created from calcium alginate round dots of around 2.5 mm in distance across and can be created by including sodium alginate arrangement into fluid arrangement of calcium chloride, coming about within the precipitation of calcium alginate, the globules are encourage isolated, snap-frozen in fluid nitrogen and freeze-dried at 400 °C for 24 h, leads to era of a permeable framework. This created framework would keep up a drifting drive for over 12 h and these drifting globules give a longer home time of more than 5.5 h[19].

Raft-forming systems

Raft-forming frameworks are in much consideration for the conveyance of stomach settling agent and sedate conveyance for gastro disease and disarranges. On contact with gastric liquid, a gel-forming arrangement swells and shapes a thick cohesive gel entangled with co2 bubbles which create pontoon layer on best of gastric liquid, in this way encourages discharges sedate gradually within the stomach [19].

Drugs which are arranged within the coasting medicate conveyance framework and their sorts of dose shapes are given within the table 3.

METHODLOGY

I. Floating tablets were prepared by the wet granulation method:-By using hydroxyl propyl methyl cellulose (HPMC K4MCR), carbopol 934P, lactose and sodium bicarbonate.

- Preparation of granules:- Granules were prepared by wet granulation method. All ingredients were accurately weighed. Then accurately weighed quantities of drug, HPMC-K4MCR, lactose, sodium bicarbonate were mixed homogeneously using glass –mortar and pestle. The wet granulation was done with ethanol (95%). Wet mass was passed through a 40-mesh screen and dried in a hot air oven at 40°C over night. The dried granules were sized through 40/60, mesh and blended with magnesium stearate (approx,1% w/w). Lactose was used as filler and channeling agent. Sodium bicarbonate was used was used as a gas generating agent, here ethanol is used as granulating agent.
- Preparation of floating tablet:- The homogeneously lubricated granules with magnesium stearate (1% w/w) were then compressed in to tablet using single punch tablet compression machine. Compression force was adjusted to obtain tablet with hardness in the range of 6.2-6.9 kg/cm2 on a Monsanto tablet hardness tester. Evaluation of blends before compression.

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Diltiazem Hydrochloride

Diltiazem is a benzothiazepine derivative with antihypertensive and vasodilating properties.Approved in 1982 by FDA it is a member of the non- dihydropyridine calcium channel blockers drug class. Diltiazem sold under the brand name Cardizem. It is taken by mouth or given by injection into a vein . When given by injection effect typically begin within a few minutes and last for a few hours Diltiazem is used to treat angina i.e. severe chest pain or hypertension (high blood pressure). High blood pressure adds to the workload of the heart and arteries. If it continues for a long time, the heart and arteries may not function properly. This can damage the blood vessels of the brain, heart, kidneys resulting in a stroke, heart failure or kidney failure. High blood pressure may also increase the risk of heart attacks. These problems may be less likely to occur if blood pressure is controlled

Side effects

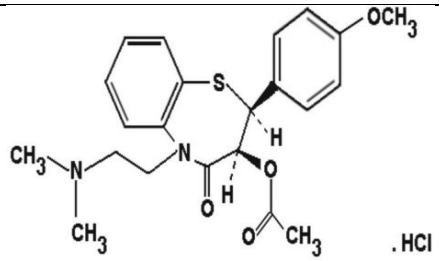
Allergic reactions: skin rash, itching, swelling of the face, tongue, or throat

Heart failure: shortness of breath, swelling of the ankles, feet, or hands, sudden weight gain, unusual weakness or fatigue

Slow heart beat: dizziness, trouble breathing, unusual weakness or fatigue

Liver injury: right upper belly pain, loss of appetite, nausea, yellowing skin or eyes, fatigue

DRUG PROFILE

NAME	Diltiazem Hydrochloride
MOLECULAR STRUCTURE	
IUPAC NAME	[(2S, 3S) -5-[2-(dimethylamino)ethyl]-2-(4methoxyphenyl)-4-oxo-2,3dihydro-1,5-benzothiazepin-3- yl] acetate;hydrochloride
MOLECULAR FORMULA	$C_{22}H_{26}N_2O_4S \cdot HCl$
MOLECULAR WEIGHT	450.98
CATEGORY	Antianginal;(calcium channel blocker)
CAS NUMBERS	33286-22-5

PLAN OF WORK

Literature Review

- Review existing formulations of diltiazem.
- Study different types of FDDS and their formulation techniques.
- Analyze the evaluation methods used in previous research.

Formulation Development

- Selection of Excipients: Choose suitable polymers (e.g., hydrophilic, gelforming) and other excipients.

Formulation Techniques:

- Matrix Tablets: Describe methods like direct compression or wet granulation.
- Hydrocolloid-based Systems: Discuss the use of hydrocolloids that swell and provide buoyancy.

Optimization: Use design of experiments (DOE) to optimize formulation parameters (e.g., polymer concentration, drug-to-polymer ratio).

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Evaluation of Formulated FDDS

Physicochemical Characterization:

- Tablet hardness, thickness, and weight variation.
- Moisture content and solubility studies.

Buoyancy Studies:

- Assess floating lag time and total floating time.

In vitro Drug Release Studies:

- Conduct dissolution tests in simulated gastric fluid (SGF). o
- Compare release profiles with conventional formulations.

Stability Studies

- Conduct accelerated stability testing under various conditions [temperature]

FUTURE SCOPE

1. Development of novel floating platforms (e.g., hydrogels, nanoparticles) for enhanced bioavailability.
2. Investigation of combination therapy using diltiazem with other antihypertensive agents.
3. Exploration of alternative routes of administration (e.g., oral, buccal, rectal).
4. Design of personalized floating drug delivery systems based on patientspecific needs.
5. Integration of emerging technologies (e.g., 3D printing, artificial intelligence) for optimized formulation and manufacturing.

II. CONCLUSION

It was possible to successfully prepare gastroretentive drug delivery devices for Diltiazem HCI. It was found that the floating lag time decreased as the amount of floating agent increased. All formulations exhibi ted better fitting with zero order release kinetics at substantially higher viscosity polymer grade, and n values indicate that all formulations followed case II transport anomalous (nonfickian) diffusion. While floating lag time and drug release were unaffected in the absence of polyo x polymer, the combination of methocel K100M, methocel E6LV, and polyox polymer caused a delay in the floating time. According to all o f these findings, a high concentration of hydrophilic polymer combine d with sodium bicarbonate enhanced the longterm release of diltiazem HCI from gastroretentive floating formulations.

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