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Review Article: An analysis of the types, formulation approach and evaluation of Betahistine floating tablets for treating Meniere's disease

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ABSTRACT
The vestibular system is frequently affected by debilitating diseases likeMeniere's disease.Unfortunately, sedative medications are frequently employed in treatment, which hinders vestibular compensation.Betahistine is the drugs which is effectively used in the treatment of the Meniere's disease. An analogue of histamine, betahistine has weak agonist actions at histamine H1 receptors and stronger antagonistic effects at histamine H3 receptors.
The main issue with oral medicine delivery is the unstable and low drug bioavailability. The Betahistine floating tablet remains in the upper part of GIT for the longer period of time releasing the drugs for prolong period of time for the treatment of Meniere's disease.
KEYWORDS: Meniere's Disease, Betahistine, Bioavailability, GIT(Gastro Instestinal Tract), Vestibular

I. INTRODUCTION

The primary goal of designing an Gastric retention drug delivery system (GRDDS) should be to increase the bioavailability of medications and make it more predictable.Drugs that are absorbed from the stomach, those that are poorly soluble or destroyed by the higher pH of the intestine, and those whose absorption can be altered by changes in gastric emptying time all require gastroretention.A floating drug delivery system's major goal is to prolong the dosage form's gastric residence time by producing gas, which is followed by swelling of the system. This gel layer on the system's surface prevents the drug from releasing into the stomach, delaying the drug's absorption.Floating drug delivery systems provide advantages over alternative pill dosage forms of medications that are absorbed in the stomach, such as ferrous salts and antacids, including pharmaceuticals with a small window of absorption and a need for localised action.By floating the dosage form in the stomach for a longer time using these floating systems, the drug's bioavailability will be raised; increased patient compliance is observed due to the decreased burden of pills. Since they can stay in the stomach for a long time, effervescent floating drug delivery systems can release the medicine over a lengthy period of time. A small absorption window can be accommodated by these systems.

Histamine (HA) is a neuromodulatory transmitter that controls a number of mental processes.Although the histaminergic nerve terminals are widely distributed across the entire brain, the histaminergic neurons in mammals are only found in the tuberomammillary (TM) nuclei of the posterior hypothalamus.The postsynaptic histamine H1 and H2 receptors as well as the presynaptic histamine H3 receptors are the three different types of histamine receptors that have been discovered.One of the medications currently recommended for individuals with vestibular loss for their symptomatic treatment of vertigo, particularly in Meniere's patients, is Betahistinedihydrochloride.One of the medications currently recommended for individuals with vestibular loss for their symptomatic treatment of vertigo, particularly in Meniere's patients, is Betahistinedihydrochloride.It is a Histamine structural analogue with stronger histamine H3 receptor antagonist and less histamine H1 receptor agonist effects.While novel fundamental processes at the CNS level have just recently been discovered, some Betahistine action sites have been understood for a long time.While novel fundamental processes at the CNS level have just recently been discovered, several Betahistine locations of action are well established.

Sensorineural hearing loss accompanied by recruitment and tinnitus, as well as recurrent spontaneous episodes of rotatory vertigo spells that patients report as spinning or whirling, are all symptoms of Meniere's illness.On the affected side,

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an unpleasant feeling of fullness in the ears may also manifest.Vertigo is typically the most uncomfortable of the other Ménière's disease symptoms, at least during the acute stage, due to its unexpected nature.Vertigo attacks are frequently incapacitating and can last anywhere from a few minutes to several days.Patients find it extremely difficult to engage in regular work or social activities while experiencing vertigo attacks. Patients frequently experience nausea, and some vomit during an episode. An off-balance feeling may persist for several days and be followed by hours of sleepiness. Quality life is frequently significantly reduced. Later stages of the illness worsen quality of life due to hearing loss, sound distortion, recruitment, and tinnitus.

CLASSIFICATION OF GRDDS

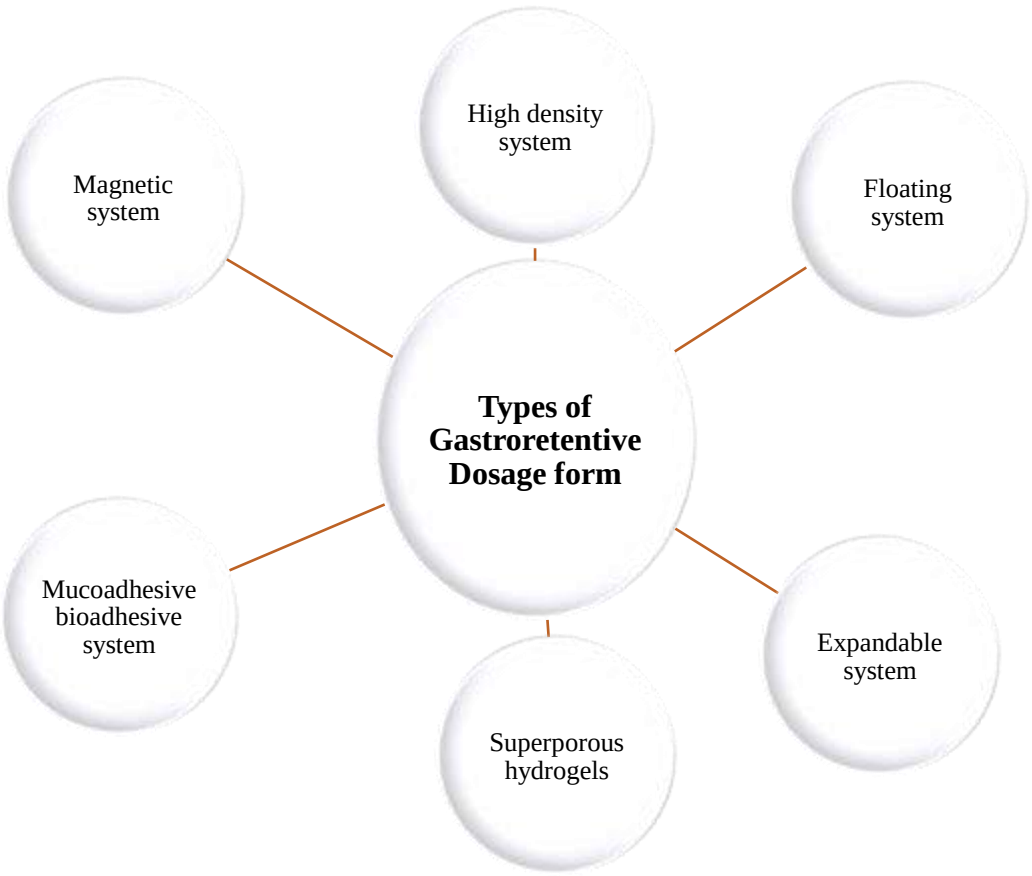

Fig: Types of Gastroretentive Dosage form

FLOATING DRUG DELIVERY SYSTEM

FDDS or Hydro-dynamically balanced systems (HBS) are low-density systems with enough tendency to float over the contents of the stomach and stay there for a long time. This allows the drug component to release at the desired rate, and while it floats over the contents of the stomach, it increases gastro-retention time and reduces fluctuation.In order to produce a medicine's pharmacological impact, the FDDS mechanism of a gastro-retentive drug delivery system regulates the pharmacokinetic release rate of a drug to a particular region.

TYPES OF FLOATING DRUG DELIVERY SYSTEM

A. **Effervescent FDDS**
1. Gas generating system
2. Volatile liquid containing system

B. **Non-Effervescent FDDS**
1. Colloidal gel barrier system
2. Bi-layer floating tablets
3. Microporous compartment system
4. Floating Beads/ Alginate Beads
5. Micro balloons/ Hollow Microspheres

C. Raft forming system

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Effervescent FDDS

A floating chamber containing air, water, vacuum, or an inert gas is used in this system. The carbonate or bicarbonate salts and the organic acid (citric acid) can react effervescingly to produce CO2, which can then be added to the floating chamber. A matrix made of swellable polymers, including chitosan-like polysaccharides, effervescent substances like citric acid, sodium bicarbonate, and tartaric acid, or chambers filled with a liquid that gasifies at body temperature are all examples of this type of system.

Gas generation system

This buoyant distribution device exploits an effervescence reaction between carbonate and bicarbonate salts and citric or tartaric acid to release CO2, further lowering its specific gravity and causing it to float over the chime.

Volatile liquid storage system

They have an inflatable chamber made of a liquid, such as cyclopentane or ether, which gasifies at body temperature to cause expansion of the chamber in the stomach. The system consists of two chambers, the first chamber containing the medicine, and the volatile liquid in the second chamber.

Non-Effervescent FDDS

The non-effervescent FDDS in the GI tract works by bioadhering to the mucosal layer of the polymer by polymer swelling. The excipients that are most frequently utilised in non-effervescent FDDS are hydrophilic gums and hydrocolloids of the cellulose type that form gels or are highly swellable.

Polysaccharides, matrix-forming substances like polycarbonate, polystyrene, polymethacrylate, and polyacrylate, as well as bioadhesive polymers like carbopol and chitosan.

Colloidal gel barrier system

In such systems, one or more gel-forming hydrocolloids of the cellulose type, polysaccharides, and matrix-forming polymers are present in large concentrations and have a high swelling potential.

Raft Forming System

Raft producing systems are frequently taken into consideration for the delivery of antacids and other drugs for gastro-infection and gastro-intestinal illnesses. The gel-forming solution expands when it comes into touch with gastric fluid, generating a viscous compact gel with trapped CO2 bubbles that forms a raft layer on top of gastric fluid and releases the medication material into the stomach over time.

Micro porous compartment systems

Based on this technology, a drug reservoir is enclosed inside a small, porous space that has perforations running the length of its top and bottom walls.

Micro balloons/Hollow microspheres

Hollow microspheres, commonly referred to as micro balloons, were discovered to float in vitro for 12 hours when submerged in aqueous solution.

Bi-layer floating tablets

The immediate release layer of a bi-layer tablet releases the initial dose from the system. The sustained release layer absorbs stomach fluid, forming an impermeable colloidal gel barrier on its surface, and maintaining a bulk density of less than 1.

Development Techniques For Betahistine Floating Drug Delivery Systems

Direct Compression techniques

It entails immediately compressing tablets made ofBetahistine powder without changing the substance's original physical makeup. The most frequently utilised carriers are dicalciumtrihydrate phosphate, tricalcium phosphate, etc.

Wet granulation techniques

Involves grinding, drying, or mixing wetBetahistine powder. Instead of compacting the powders, wet granulation forms the granules by joining them using an adhesive.

Solvent evaporation techniques

The amount of liquid dispersal solvent that can be removed during a continuous phase is insufficient. The dispersal surface's solvent evaporates, allowing hardened microspheres to be absorbed.

Effervescent techniques

Citric acid and bicarbonate salts will react in an effervescent manner to produce inert gas, which will then fill the floating chamber of the medication delivery system (CO2).

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Ionotropic Gelation Technique

The basic polymer of natural origin, anionic polysaccharide sodium alginate, was gelated with oppositely charged calcium ions (counter-ions) in order to create instantaneous microparticles.

Melt Solidification Technique

The molten material is emulsified in the aqueous phase using this technique, and then it is cooled to solidify. The carriers employed for this approach include lipids, waxes, polyethylene glycol, etc.

Melt Granulation Technique

Using a meltable binder, this technique granulates the medicinal powders without the need of water or organic solvents.

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

- Beneficial for medications intended for localised effect in the stomach, such as antacids.
- In cases of diarrhoea and intestinal movement, the FDDS formulation helps keep the medication in a floating state in the stomach for a more favourable response.
- As FDDS can stay in the stomach for several hours, it increases the amount of time that different medications are retained in the stomach.
- By reducing the frequency of dose, FDDS raises patient compliance.
- Delivery of the medication to the designated location.
- Favourable for medications that are absorbed through the stomach For instance, iron salts and antacids.

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

- Food must typically be present in these systems in order to delay stomach emptying.
- It is not appropriate for medications that have GIT solubility or stability issues.
- The dosage form's level of hydration affects its propensity to float. It's helpful to administer water intermittently to keep these tablets afloat.
- Drug compounds that are unstable in the stomach's acidic environment are not good candidates for system integration.
- It is not appropriate for medications that have GIT solubility or stability issues.

PREFORMULATION STUDIES

Solubility studies

In order to conduct the solubility tests, 1 g of betahistine was dissolved in 10 ml of water, ethanol, methanol, dichloromethane, and hexane.

Determination of Melting Point

Melting point of Betahistine was determined by capillary method. Fine powder of Betahistine was filled in glass capillary tube (previously sealed on one end). The melting point is determined by using digital melting point apparatus.

Compatability studies by FTIR spectroscopy

Compatibility with excipients was confirmed by carrying out IR studies. The pure drug and its formulations with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Angle of repose

The fixed funnel and free standing cone method employed a funnel that was secured with its tip at a given height H, above graph paper that was placed on a flat horizontal surface. Powder or granules was carefully poured through the funnel until the apex of the conical pile just touch the tip of the funnel. Thus with R being the radius of the base of the conical pile.

$\tan \alpha = H/R$ (Where, α is the angle of repose)

Bulk density

It was determined by pouring pre-sieved (40-mesh) bulk drug into a graduated cylinder via a large funnel and measuring the volume and weight as:

$\delta b = M/Vb$

Carr's index

It can be the measure of the potential strength that a powder could build up in its arch in a hopper and also the ease with which such an arch could be broken.

Carr's index= (Tapped density – Bulk density)/Tapped density * 100%

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Hausner ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula:

$H = \delta t/\delta b$

Where,

δb is the freely settled bulk density of the powder,

δt is the tapped density of the powder.

POST-COMPRESSION EVALUATION

Floating lag time and floating time

In vitro buoyancy was determined by measuring lag time and duration of floating. The tablet were placed in a 250ml glass beaker containing citric acid buffer pH 3 the time required for the tablet remain floating was determined as floating time required for the tablet to raise to the surface and the float was determined as floating lag time .the duration in which the tablet remain floating was determined as floating time.

Buoyancy lag time (BLT)

On immersion of tablets of different formulations in 0.1N HCl solution at 37±5°C, the tablets floated, and remained buoyant without disintegration.

Weight variation test

➢ Weight variation test was done by weighing 20 tablets individually.

➢From this total weight average weight is calculated.

➢ Percentage weight variation is calculated by using following formula:

Percentage Deviation PD= $(W_{Individual}-W_{Average})/ W_{Average} \times 100$

Where,

$W_{Individual}$=Weight of individual tablet

$W_{Average}$= Average weight of tablet

Tablet hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. Several devices operating to test tablet hardness are: Monsanto tester, Pfizer tester.

Tablet thickness

Thickness of the tablet is measured by using verniercalliper. Thickness should not deviate ±5% from standard value.

Friability Test

➢The friability of the tablets was measured in a Roche Friabilator.

➢ Tablets of a known weight (W0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again.

➢ Percentage friability was calculated from the loss in weight as given in equation as below.

➢The weight loss should not be more than 1 %.

➢ Determination was made in triplicate.

% friability= $(W_O-W)/W \times 100$

Where,

W_O= Initial weight

W= Weight after friability

Drug content

➢Five tablets were taken and amount of drug present in each tablet was determined.

➢The tablet was crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask.

➢The powder was diluted upto the mark with citric acid buffer pH 3.

➢This solution was diluted suitably and analyzed for drug content by UV spectrophotometer at 276nm using citric acid buffer pH-3 as blank.

In-Vitro drug release studies

The release rate from floating tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 100 rpm. A sample (5ml) the solution was withdrawn from the dissolution apparatus hourly for 24h, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 284nm using a Shimadzu UV-Vis double beam spectrophotometer 1800. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Swelling index of Betahistine floating tablet

The swelling index of tablets was determined by using 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals.

The swelling index was calculated by the following equation:

Swelling index (SI) $=(W_t-W_o)/ W_o \times 100$

Where, W_t= Weight of tablet at time t.

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W_0 = Initial weight of tablet.

II. CONCLUSION

Hence, a variety of techniques were employed to create the ideal gastro retention, but the floating drug delivery system has emerged as the most promising one for the Betahistine floating tablet for the treatment of Meniere's disease.These systems improve the bioavailability and regulated distribution of drugs with new and important treatment possibilities by improving the absorption of medications that are absorbed from the top section of the stomach.Less frequent dosing and improved therapy effectiveness are the results of this.Such a technology is more reliable since it has superior medication release and stability than other standard dose forms.A prolonged GI retention of the dose form extends the time of medication absorption because the GIT is an incredibly changeable system.A technique for stomach retention is guaranteed by the floating drug delivery system.

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