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Formulation Development and Evaluation of Gastro Retentive Floating Tablet of Albendazole

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ABSTRACT

The formulation of floating tablet CMC and albendazole used as matrix forming agent, other excipient used are sodium bicarbonate {as a gas generating agent} citric acid, magnesium stearate as a lubricant. The drug subjected to various preformulation studies such as angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio characterization using FTIR, drug, and excipient compatibility the tablet were using single station punching machine. The prepared tablet was subjected to various evaluation parameters such as thickness, hardness, weight variation, friability buoyancy study and *in vitro* drug release, it was concluded that there was no interference in the functional group as the principal peak of the drug were found to be unaltered in the drug physical mixture.

INTRODUCTION:

The oral route is increasingly being used for the delivery of therapeutic agents because the low the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available delivery systems.

The oral route is the predominant and most preferable route for drug delivery, but drug absorption is unsatisfactory and highly variable in the individuals despite excellent *in-vitro* release patterns. Drug delivery to the upper small intestine window using gastroretentive technologies. The major problem is in the physiological variability such as gastrointestinal transit as well as GRT (gastric residence time); the later plays a dominating role in overall transit of the dosage forms. GRT (gastric residence time) of the oral controlled release system is always less than 12h. Gastroretention a means to address regional variability in intestinal drug absorption. These aspects lead to the development of a drug delivery system which will remain in the stomach for a prolonged and predictable time.

Drug targeting to the stomach can also be attractive for several other reasons:

• For drugs which have poor stability in the colon.

• For drugs which have a narrow absorption window.

• For the drugs which have primarily absorption in the stomach.

From the formulation and technological point of view, FDDS (floating drug delivery system) is a considerably easy and logical approach in the development of GRDF (gastroretentive dosage form). Hence, this review article focuses on the current technological development in FDDS with special emphasis on its potential for oral controlled drug delivery.

Gastrointestinal tract physiology:

Stomach

The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm. Its size varies according to the amount of distension: up to 1500 ml following a meal; after the food has emptied, a collapsed state is obtained with resting volume of 25–50 ml. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus) (shown in figure 1). The proximal stomach, made up of fundus and body regions,

serves as a reservoir for the ingested materials, while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying.

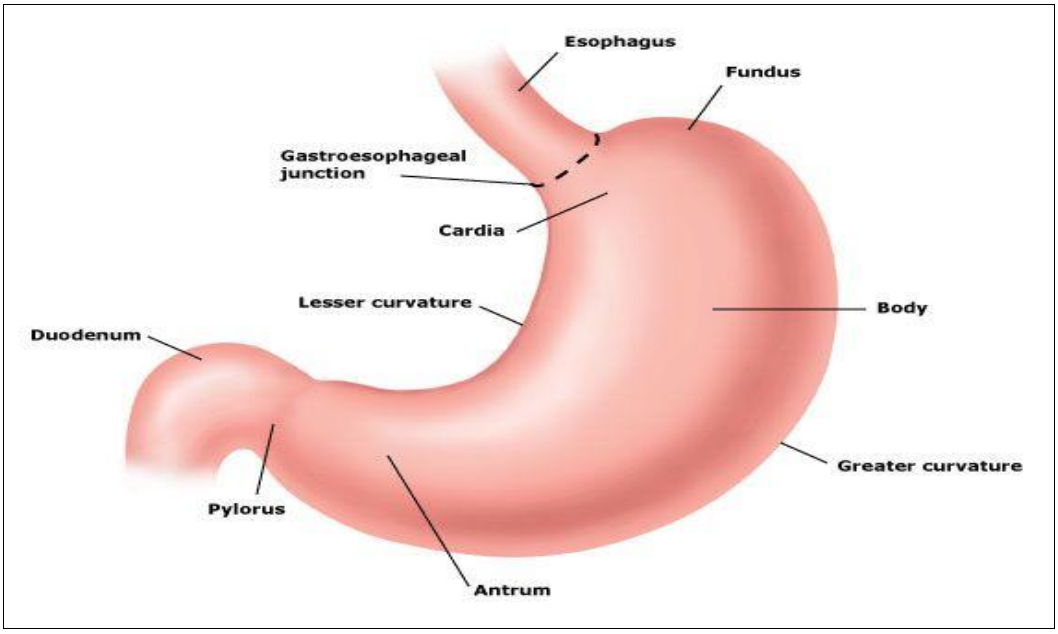

Figure 1: Anatomy of stomach

Gastrointestinal motility:

Two distinct patterns of gastrointestinal motility and secretion exist corresponding to the fasted and fed states. As a result, the bioavailability of orally administered drugs will vary depending on the state of feeding. In the fasted state, it is characterized by an inter-digestive series of electrical event and cycle, both through the stomach and small intestine every 2–3 h. This activity is called the *interdigestive myoelectric cycle* or Migrating motor complex (MMC). MMC is often divided into four consecutive phases: basal (Phase I), pre-burst (Phase II), burst (Phase III), and Phase IV intervals.

- Phase I (basal phase) lasts from 40–60 min with rare contractions.

- Phase II (pre-burst phase) lasts for 40–60 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increase gradually.

- Phase III (burst phase) lasts for 4–6 min. It includes intense and regular contractions for short periods. Due to this contraction, all the undigested material is swept out of the stomach down to the small intestine. This is also known as the housekeeper wave.

- Phase IV lasts for 0–5 min and occurs between phases III and I for two consecutive cycles.

The motor activity in the fed state is induced 5–10 min after the ingestion of a meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2–6 h, and more typically 3–4 h, with phasic contractions similar to Phase II of MMC.

Problems associated with the absorption from the oral route

There are many of the factors which affect the absorption of oral dosage form like Bioavailability Problem, Extended Dosage Regimen, First Pass Metabolism, Gastric Emptying Time, and Effect of PH on Drugs, Absorption Windows, and Enzymatic Degradation in Gastrointestinal Tract. [1-8].

Approaches to overcoming the problem related to oral dosage forms

The pharmaceutical approach involves modification of formulation, manufacturing process or the physicochemical properties of the drug without changing the chemical structure.

The pharmacokinetic approach causes an alteration by modifying its chemical structure. This approach is further divided into two categories- Development of new chemical entity with desirable features and Prodrug design.

The biological approach whereby the route of drug administration may be changed such as from oral to parenteral route. [9]

Pharmaceutical approaches are mainly used for overcoming the problem related to other oral drug delivery system. Recently Sustained Release & Control Release Drug Delivery System is preferred.

Sustained & Controlled Release Drug Delivery System

The sustained release system is a slow release system in which the drug is slowly released from the dosage form but not predictable. Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time. Continuous oral delivery of drugs at predictable & reproducible kinetics for a predetermined period throughout the course of the gastrointestinal tract.[10,11] Those are the advancements

made in other drug delivery systems in order to increase the clinical efficacy and patient compliance. Controlled drug delivery systems are of many types.

Recently the gastroretention is a major approach to overcoming the problem related to other oral drug delivery system.

Gastroretentive Drug Delivery Systems:

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [12].

Need for Gastroretentive Drug Delivery System:

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, the material passes through the small intestine in as little as 1-3 hours. Gastroretentive systems useful for drugs acting locally in the stomach (Antacids and drugs for H. Pylori viz., Misoprostol), Drugs that are primarily absorbed in the stomach (Amoxicillin), Drugs that is poorly soluble at alkaline pH (Furosemide, Diazepam, Verapamil), Drugs having narrow absorption window (Cyclosporine, Methotrexate, Levodopa), Drugs which are absorbed rapidly from the GI tract (Metronidazole, tetracycline), Drugs that degrade in the colon (Ranitidine, Metformin HCl), Drugs that disturb normal colonic microbes (antibiotics against Helicobacter pylori).[13, 14].

1.3 Types of gastroretentive system

1. **High-density system**

2. **Modified shape system**

3. **Mucoadhesive system**

4. **Floating drug delivery system**

1. High-Density System -Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture [15].

2. Modified Shape Systems/ Unfolding Systems- These are the dosage forms, which after swallowing, swell to an extent that prevent their exit from the pylorus. As a result, the dosage form is retained for a longer period of time [16].

3. Mucoadhesive Systems -Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bioadhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric-retention [17]. Materials commonly used for adhesion are polyacrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).[18].

4. Floating Drug Delivery System- Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time.

Floating drug delivery system

The floating drug delivery system is also known as a hydrodynamically balanced system (HBS). While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of the drug, the residual system is emptied

from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration [19].

Advantages of FDDS

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:-

1) Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.

2) Controlled delivery of drugs.

3) Delivery of drugs for local action in the stomach.

4) Minimizing the mucosal irritation due to drugs, by drug releasing slowly at a controlled rate.

5) Treatment of gastrointestinal disorders such as gastroesophageal reflux.

6) Simple and conventional equipment for manufacture.

7) Ease of administration and better patient compliance.

8) Site-specific drug delivery. [20].

Limitations of FDDS

1) Gastric retention is influenced by many factors such as gastric motility, pH and the presence of food. These factors are never constant and hence the buoyancy cannot be predicted.

2) Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

3) High variability in gastric emptying time due to its all or non-emptying process.

4) Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed. [21].

Factors affecting the floating and floating time-

1. **Density:** Floating is a function of dosage form buoyancy that is dependent on the density. Density o ft he dosage form should be less than the gastric contents (1.004gm/ml).

2. **The shape of dosage form:** Dosage form unit with a diameter of more than 7.5 mm is reported to have an increased GRT competed with those with a diameter of 9.9 mm. Tetrahedron and ring-shaped devices with flexural modules of 48 and 22.5-kilo pounds per square inch (psi) are reported to have better floating, 90% to 100% retention at 24 hours compared with other shapes.

3. **Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.

4. **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs in every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

5. **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

6. **Caloric content and feeding frequency:** Floating can be increased by four to 10 hours with a meal that is high in proteins and fats. The floating can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

7. **Age:** Elderly people, especially those over 70, have a significantly longer; floating. Disease condition such as diabetes and Crohn's disease etc also affect drug delivery.

8. **Gender:** Mean ambulatory GRT in males (3.4 0.6 hours) is less compared with their age and race-matched female counterparts(4.6 1.2 hours), regardless of the weight, height and body surface.

9. **Posture:** Floating can vary between supine and upright ambulatory states of the patient [22,23].

Approaches to design a floating drug delivery system

Practical approaches to designing FDDS

The concept of FDDS was first described in the literature as early as 1968 when Davis (1968) disclosed a method to overcome the difficulty experienced by some persons of gagging or choking after swallowing medicinal pills.

Approaches to design single and multiple unit dosage forms

1. Single Unit Dosage Form

2. Multiple Unit Dosage Form

1. Single Unit Dosage Form-

In low-density approaches, the globular shells apparently having a lower density than that of gastric fluid can be used as a carrier like popcorn, poprice, polystrol for the drug for its controlled release. The polymer of choice can be either Ethylcellulose or CMC depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid-filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses as a reservoir having apertures present at the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. Hydro Dynamically Balanced Systems are designed to prolong the stay of the dosage forms in the gastric intestinal tract and aid in enhancing the absorption. Drugs having a better solubility in an acidic environment and also having a specific site of absorption in the upper part of the small intestine is achieved by these HBS systems. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than ‘1' and has to maintain its structural integrity and release drug constantly from the dosage form. Among all the advantages single-unit formulations are associated with some limitations/problems such as sticking together or being obstructed in the GIT which may lead to the potential danger of producing irritation [25].

MATERIALS AND METHODS:

METHODS:

The Preformulation studies were performed to have sound knowledge about the drug. Preformulation may be described as authenticating the drug by the determination and/or definition of their physical and chemical properties, which are considered an important factor in the formulation of a stable, effective and safe dosage form. Preformulation data must be generated to serve as a basis for the design of a delivery system to achieve optimum stability and maximum bioavailability thus, in order to establish an optimum condition for developing suitable drug delivery system, following Preformulation studies were carried out.

Wet granulation method:

Tablets were prepared by conventional wet granulation method. The various excipients used were listed in Table No. 13. Ingredients except glidants and lubricant were thoroughly mixed and passed through sieve no. 60. Granulation was done with a solution of calculated quantity of PVP K30 in sufficient isopropyl alcohol. The wet mass was prepared passed through sieve no. 12 and dried at 50 °C for 2 h. The dried granules were lubricated with magnesium stearate and talc and compressed into tablets using a single station tablet punch machine.

Table 2: various formulations of Albendazole Gastro retentive Floating tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Albendazole	400	400	400	400	400	400	400	400	400
HPMC K 15	_	_	_	100	120	130	50	60	65
HPMC K 4	100	120	130	_	_	_	50	60	65
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	50	30	20	50	30	20	50	30	20
Total Weight	600	600	600	600	600	600	600	600	600

Evaluation of the gastro-retentive tablet blend:

Table 3: Characters of the blend on various parameters (F1-F5) of Albendazole:

Material	The angle of repose (degree)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr index	Hausner ratio	FLT (sec)
F1	26.2 ±	0.40	0.49	15.57	1.05	44
F2	22.29 ±	0.50	0.58	11.59	1.16	47
F3	33.08 ±	0.48	0.56	18.54	1.28	32
F4	22.58±	0.39	0.49	7.59	1.01	54
F5	28.35±	0.42	0.52	15.18	1.11	63

Evaluation of tablet

Weight variation test:

Tablet weight is mainly affected by factors such as tooling of the compression machine, head pressure, machine speed and flow properties of the powder. Inconsistent powder or granulate density and particle size distribution are a common source of weight variation during compression. Variation between a tablet with respect to dose and weight must be reduced to a minimum. Uniformity of weight is an in-process test parameter which ensures consistency of dosage units during compression.

Procedure:

10 tablets were selected at a random and average weight was determined. Then individual tablets were weighed and were compared with average weight.

Test for Uniformity:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes.

Procedure:

Two tablets were placed in a 100ml of water and stirred until completely dispersed. A smooth dispersed produced through passed through a sieve screen with a nominal mesh aperture of 710 mm (20 meshes). The formulation posses the values within the official limit.

DRUG CONTENT ESTIMATION:

The drug content uniformities used to measure tablet drug amount in certain limitations.

Procedure:

10 tablets were taken their weight accurately. Average weight is calculated and equivalent to 25mg of a drug was taken for estimating the drug content in the total tablet. It was within the official limit.

Percentage of drug content is calculated by **Y/X x 100**

Where Y= Actual drug content (mg)

X= labeled amount of drug (mg).

Friability

Procedure:

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effects of abrasions and shock in plastic chamber revolving at 25 rpm and dropping the tablets at heights of 6 inches in each revolution. A preweighed sample of the tablet was placed in the friabilator and was subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. (48).

The friability (f) is given by the formula:

$$F= (I - Wo / W) \times 100$$

Where

Wo- is the weight of the tablets before the test

W-is the weight of the tablets after the test.

Hardness

Tablet hardness testing is a laboratory technique used by the pharmaceutical industry to test the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage"[1] The breaking point of a tablet is based on its shape.[2] It is similar to friability testing,[1] but they are not the same thing.

Tablet hardness testers first appeared in the 1930s.[3] In the 1950s, the Strong-Cobb tester was introduced. It was patented by Robert Albrecht on July 21, 1953.[4] and used an air pump. The tablet breaking force was based on arbitrary units referred to as Strong-Cobbs.

Procedure:

Hardness or tablets crushing strength (FC) (the force required to break a tablet in a diametric compression) was measured using the MONSANTO tablet hardness tester.

Thickness:

The individual crown-to- crown thickness of 10 tablets determined using a slide caliper for each batch. The sample mean and standard deviation of each batch tablets were calculated.

Disintegration:

Disintegration time was determined using the disintegration apparatus USP (E.I. instrument, Haryana India) in 0.1N HCl for 2h and then in phosphate buffer pH 6. Maintaining the temperature at 37+_ 2C.

Procedure:

Put in distilled water for five minutes to dissolve the coat. Then put in simulated gastric fluid (0.1N HCl) for one hour. Then put in simulated intestinal fluid for two hours. If one or two tablets fail to disintegrate, repeat this test on another 12 tablets.

Floating Lag Time

The lag time was carried out in a beaker containing 100ml of 0.1 N HCl as attesting medium maintained 37^{o}C the time required for the tablet to rise to the surface and flow was determined as floating lag time.

Buoyancy time

Floating time was determined by using IP tablets dissolution apparatus at 50rpm using 900ml of 0.1 N HCl at 37+ 0.5 C Temperature the floating duration was the time during which the tablet remains buoyant and floating lag time was the time between tablet introduction and its buoyancy. Duration of floating and floating lag time was measured by visual observation.

Dissolution rate study:

In vitro dissolution studies for all the fabricated tablets and the pure drug was carried out the USP paddle method at 50rpm in 900ml of phosphate buffer pH 5.8. maintained at 37+_ 0.5 ml of aliquots withdrawn at specified intervals filtered Whatman filter paper and analyzed at 243nm using UV-Visible spectrophotometer. The dissolution media was then replaced by 5ml of each fresh dissolution fluid to maintain a constant volume.

Table 4: dissolution profile of Albendazole floating tablet

Time (hr)	F1	F2	F3	F4	F5
1	19.59	20.68	18.45	16.95	14.38
2	26.38	21.38	25.85	22.78	18.19
3	33.52	32.85	33.36	39.25	31.58
4	50.25	46.29	48.22	42.52	40.18
5	62.25	58.52	63.38	66.34	57.68
6	72.22	76.25	78.23	82.05	79.58
8	80.65	77.25	78.65	82.06	72.54
10	84.03	80.58	85.36	89.52	88.67

CONCLUSION

Floating tablets used for the drug which get easily solubilized in stomach Albendazole floating tablets was used for the treatment of anti-worm medication or parasites. A drug which is having low oral bioavailability (<5%), longer biological half-life (about 8 to 12 hours) and adequate protein binding that are preferred while formulating a floating tablet. On the basis of finding observed in present work, it can be concluded that floating tablet of Albendazole is the suitable dosage form for the treatment of anti-worm medication or parasites with low dosing frequency for better patient compliance, less toxic & better anti-worm medication than other floating tablet formulations. This dosage form is preferred as it is very convenient and easy to formulate. Cost- effective and does not require high-cost equipment. For that reason, this dosage form has been gaining so much attention nowadays. From the above experimental result, it can be concluded that sodium bicarbonate has a predominant effect on the buoyancy lag time, while CMC has a predominant effect on the total floating time and drug release.

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