

**FORMULATION, OPTIMIZATION AND INVITRO EVALUATION OF GASTRO
RETENTIVE SUMATRIPTAN SUCCINATE TABLETS****G. Pratap Kumar*, Venkata Naga Swetha M. and T. Murali Krishna**

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ABSTRACT

The present work was aimed at developing effervescent floating tablets of Sumatriptan succinate using natural and synthetic polymers. Gas generating agents and diluent, glidant and lubricants are used in Sumatriptan succinate floating tablets with effervescent method were also formulated. Migraine is a common disorder characterized by a unilateral headache, which is often associated with nausea, vomiting, gastrointestinal disturbance and extreme sensitivity to light and sound. Sumatriptan succinate is the first member of a new class of anti-migraine compounds that act as a specific and selective 5-hydroxytryptamine-1 receptor agonist. Sumatriptan has low bioavailability after oral administration (about 15%), with a large inter-individual variation, although not affected by concomitant food intake. The dose is 50-100 mg orally. T_{max} is reached at approximately 2 h and is slightly delayed by the presence of food and during an acute migraine attack. Sumatriptan succinate, an anti migraine agent, has been widely used for the treatment of anti migraine. It has been reported, however, that the duration of anti migranic action after a single oral dose of sumatriptan succinate is only 2-4 hr. Clinical use requires a dose of 50-100 mg to be taken once a day but NMT 200mg/day. Sumatriptan succinate has a pH of 1.2 & remains stable at stomach environment. Frequency of dosing will be minimized. **Objectives:**

1. To increase patient compliance by preventing repetitive administration of the dosage forms.
 2. To prolong drug release in a sustained manner using HPMC-K4M as the rate controlling polymer
- To increase the gastric residence time of Sodium bicarbonate by developing floating drug delivery systems. To evaluate the prepared dosage forms by carrying out suitable quality control tests.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for delivery of drugs via pharmaceutical products of different dosage forms. Oral route is considered as the most natural, uncomplicated, convenient and safe due to its easy of administration, patient acceptance and cost-effective manufacturing process.

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

- 1) Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.
- 2) A typical peak-valley plasma concentration-time profile is obtained which makes difficult to attainment of steady state condition.
- 3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{ss} values fall or rise beyond the therapeutic range.

- 4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have lead to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

- 1) Delayed release
- 2) Sustained release
- 3) Site-specific targeting
- 4) Receptor targeting

More precisely, Controlled delivery can be defined as:-

- 1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effect.
- 2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
- 3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
- 4) Provide a physiologically/ therapeutically based drug release system. In other words, the amount and rate of drug release are determined by the physiologically/therapeutic needs of the body.
- 3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
- 4) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- 5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

Advantages of Controlled Drug Delivery Systems

- A) Avoid patient compliance problems.
- B) Dosage frequency were reduced
 - 1) Minimize or eliminate local side effects
 - 2) Minimize or eliminate systemic side effects
 - 3) Obtain less potentiating or reduction in drug activity with chronic use.
 - 4) Minimize drug accumulation with chronic dosing.
- a) Improve efficiency in treatment
 - Cures or controls condition more promptly.
 - Improves control of condition i.e., reduced fluctuation in drug level.
 - Improves bioavailability of some drugs.
 - Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.

Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

Disadvantages

- 1) Decreased systemic availability in comparison to conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
- 2) Poor in vitro-in vivo correlation.

Gastro Retentive Dosage Form (GRDF)

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDS or GRDF).

Some drugs tend to be absorbed in specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical stability, the binding of the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon. Physiological factors like gastrointestinal transit time, regional pH, surface area, enzymatic activity and colonic micro flora influence drug absorption and some of these factors may be used to achieve control over drug absorption. In vitro receptor binding assays in drug delivery had shown to increase the proportion of lower permeability drugs developed which often results in selection of either multiplied ionized peptide mimetic or more soluble and hydrophobic drugs having improved partitioning into the hydrophobic pockets of protein receptors.

Delivery of drugs at a specific region in gastrointestinal tract, these so called absorption window needs the development of gastro retentive dosage forms. The attempts to develop gastro retentive drug delivery systems may be largely divided into two classes: those that rely on the natural physiology of the gastrointestinal tract and those that are designed to overcome it. Approaches such as size or floatation, which rely on delayed emptying from the stomach, depend on the normal physiological duration of the fed state of 4-8 hr, following a meal and rather reproducible transit time through the small intestine.

The transit time of a dosage form through the gastrointestinal tract is variable or even unpredictable, and can be of very short duration due to this the time available for the drug absorption might be short and limits the absorption of drugs which are absorbed at certain sites along the gastrointestinal tract. The concept of Floating Drug Delivery System was described as a method for overcoming the difficulty experienced by some people of gagging or choking while swallowing medicine pills. It was suggested that this difficulty could

be overcome by providing pills having density of less than 1.0 gm/ml, so that pills will float on water surface. Since then many types of gastric retention drug delivery systems were tested to overcome the limited region and times for drug absorption in gastrointestinal tract.

The main approaches that have been examined for gastro retentive dosage forms (GRDFs) are: low density of GRDF that cause buoyancy above gastric fluid (Floating system), high density which retain the dosage form in the body of stomach, concomitant administration of drugs or excipients which slow the motility of the GIT, bio adhesion to gastric mucosa, swelling to a large size which prevent emptying of dosage form through the pyloric sphincter.

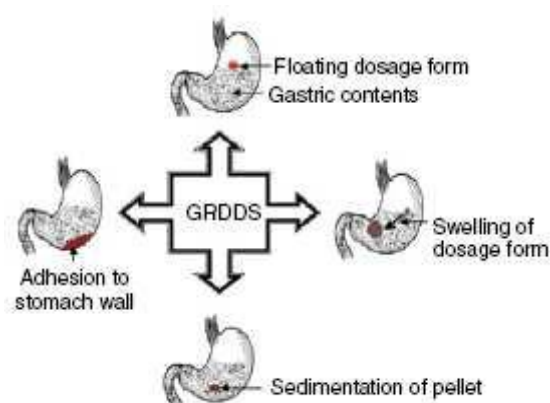


Figure 1: Classification of gastro retentive drug delivery system

Gastrointestinal Tract Physiology

The anatomy and physiology of gastrointestinal tract Figure 2 is very complex with variations in acidity, bile salts, enzyme content and mucosal absorptive surface from mouth to the rectum. These variations significantly influence the drug release, dissolution and absorption from orally administered dosage forms. The stomach is divided into three anatomical regions: fundus, body and pylorus (or antrum). The proximal part is made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Pyloric sphincter has a diameter of 12.8 ± 7 mm in human and acts as a sieve as well as mechanical structure to the passage of large particles.

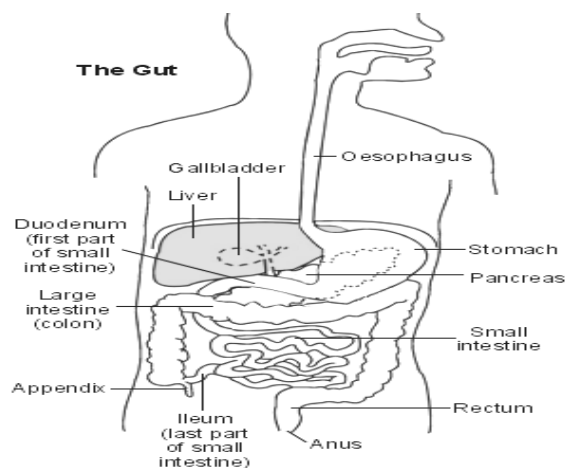


Figure 2: Gastrointestinal Tract: General

1. Body of stomach
2. Fundus
3. Anterior wall
4. Greater curvature
5. Lesser curvature
6. Cardiac
9. Pyloric sphincter
10. Pyloric antrum
11. Pyloric canal

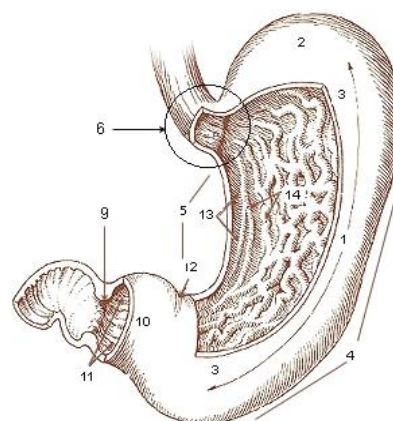


Figure 3: Schematic diagram of stomach

Table 1: Characteristics of Gastro Intestinal Tract

Section	Area (m ²)	Average length (cm)	Liquid Secretion (l/d)	Reaction (pH)	Absorption Mechanism	Major constituents	Transit time (hr)
Oral cavity Esophagus	About 0.05	15-20 25	0.5-2	5.2-6.8	Passive diffusion, convective transport.	Amylase Ptyalin Mucin	Short
Stomach	0.1-2	20	2-4	1.2-3.5	Passive diffusion, convective transport.	Hydrochloric acid Pepsin Rennin Cathepsin Lipase Intrinsic factor	0.2-3

Duodenum	About 0.04	25	1-2	4.6-6.0	Passive diffusion, convective transport. Active transport, facilitated transport, Ion pair, pinocytosis.	Bile, trypsin, chymotrypsin, amylase, maltase, lipase, nuclease, CYP3A4.	1-2
Small Intestine							
Jejunum	4500	300	0.2	4.7-6.5	Passive diffusion, convective transport, Active transport, facilitated transport.	Like in duodenum	1-10
Ileum		300					
Large intestine							
Cecum	0.5-1	10-30	About 0.5	7.5-8.0	Passive diffusion, convective transport. Active transport, pinocytosis.	Mucus, bacterium.	4-20
Colon		150					
Rectum		15-19					

Gastro Intestinal Motility

The gastric motility is in the form of forced contractions and is responsible for grinding the food into smaller particles, mixing it with gastric juices, forward and backward movements of gastric contents and emptying, with all of the actions occurring together. There are three basic mechanism of contractile activity of gastrointestinal smooth muscles: **Myogenic**, **neural** and **chemical**. These mechanisms work together to coordinate contractile activity within each segments of the gastrointestinal tract.

Myogenic control refers to the properties of the smooth muscle membrane potential which are different in the proximal and distal stomach.

- **Electrical control activity (ECA)/ Basic Electrical Rhythm/ Pacemaker Potential:** It is smooth muscle membrane potential characterized by an omnipresent oscillation in the distal 2/3 of the stomach. In this region it controls the maximum frequency at which contraction can occur at a site as well as the phase relationship of contraction at adjacent sites.
- **Electrical response activity (ERA):** It is the second type of response activity which occurs when the excitatory neural or chemical input is present during the depolarization phase of an ECA cycle. During this the membrane potential reaches the excitation threshold. ERA is also referred to as spike bursts or an action potential.

In the stomach the cells with the highest ECA frequency and membrane potential are located midcorpus, along the greater curvature and cycle at 3/min in man and 5/min in dogs. This area is called as pace setter region. The cells distal to this region have a progressively more negative resting membrane potential and a slower ECA frequency allowing them to be driven by the pacesetter region. From the pacesetter region, ECA propagates abroad and is somewhat faster along the greater curvature than along the lesser curvature.

This results in the proximal stomach having mainly tonic activity and allows it to function as a reservoir following a meal. In the pylorus the outer one third of the smooth muscle exhibits spontaneous activity. This results in the pylorus having both phasic contractions as well as tonic contractions. In the duodenum the pacesetter region is located in the duodenal bulb and cycles at about 12/ min in human and 18/min in dog. As in the stomach, ECA does not cause contraction of the smooth muscle but controls the maximum but controls the maximum frequency at which contractions can occur.

Neural control refers to the extrinsic and intrinsic nerves that innervate the gut. The extrinsic nerves arise from the vagal and splanchnic fibers. Vagal efferents are both excitatory and inhibitory. The excitatory efferents are cholinergic fibers that increase both fundic tone and antral contractions and constrict the pylorus. The inhibitory fibers are noradrenergic and noncholinergic, cause fundic relaxation and inhibitions of antral contractions and relax the pylorus. The splanchnic neurons are adrenergic fibers that also cause fundic relaxation and inhibition of antral contractions and relax the pylorus. The intrinsic innervation of the stomach and small intestine is composed of two major plexuses the myenteric and submucosal and several minor ones and they play a major role in controlling the spatial and temporal patterns of contractions by integrating central and peripheral neural input.

Chemical control refers to the release of substances from endocrine/ paracrine cells, immune cells, and endocrine glands that modulate contractile activity. These substances can also be both excitatory and inhibitory and act either directly on the smooth muscle or through activation of neural systems.

There are two modes of gastrointestinal motility in human and animals that consume food on a discrete basis; the digestive fed mode and the inter digestive fasted mode. The contractile motility of the stomach grinds the food particles mixes it with gastric juices,

moves gastric contents forward and backward and emptying. The fasting gastrointestinal motility is characterized by a cyclic pattern. This cyclic pattern of motility originates in the foregut and propagates to the terminal ileum clearing the stomach and the small intestine of undigested debris, swallowed saliva and sloughed epithelial cells.

Phase I: - Quiescent period with no electrical activity and no contractions.

Phase II: - The period of random spike activity or intermittent contraction.

Phase III: - The period of regular spike bursts or regular contraction at Maximal frequencies in that migrate distally.

Phase IV: - The transition period between phase III and phase I.

This cyclic pattern is called as interdigestive migratory motor complex.

Phase III is also known as house keeper wave, serves to clear the digestive tract of all indigestible material from the stomach and small intestine. Phase III activity in the antrum is characterized by groups of 3-6 contractions that gradually build in amplitude until a couple of contractions of maximal force occur.

When these contractions occur, the pylorus is relaxed and contractile activity of the duodenum is inhibited. This relaxation allows the pylorus to be stretched to its maximal aperture during emptying of indigestible particles. With the termination of each group of antral contraction, contractile activity returns to the pylorus and the duodenum along with an increase in tone of pylorus. Feeding results in interruption of the inter digestive motility cycle of the gastrointestinal tract and in appearance of a continuous pattern of spike potentials and contractions called postprandial motility. A minimum amount of gastric content appears to be necessary in order to change motility from a migratory motor complex (MMC) to postprandial. Oral administration of 150 ml of water during phase I changes the fasted motor activity to a fed like pattern in dogs.

Gastrointestinal Transit

Like the motility pattern, the pattern of GIT transit depends on whether the person is in a fasted or fed state and also the physical state of drug delivery system either a solid or a liquid. The residence time of liquid and solid is shown in Table 2:

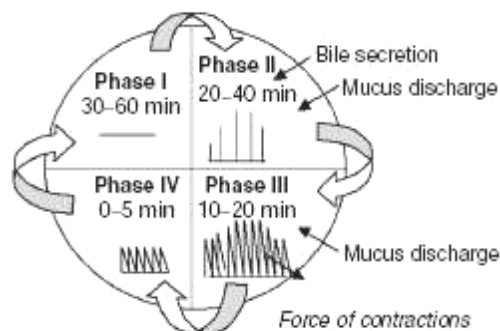


Figure 4: Motility patterns of the GIT in the fasted state

Table 2: Residence time of liquid and solid in GIT

Segment	Liquid	Solid
Stomach	10-30 min	1-3 hours
Duodenum	< 60 sec	< 60 sec
Jejunum & Ileum	3±1.5 hours	4±1.5 hours
Colon	-	25-50 hours

Table 3: Transit times of various dosage forms across the GIT

Dosage form	Gastric	Small intestine	Total
Tablets	2.7 ± 1.5	3.1 ± 0.4	5.8
Pellets	1.2 ± 1.3	3.4 ± 1.0	4.6
Capsules	0.8 ± 1.2	3.2 ± 0.8	4.0
Oral Solutions	0.3 ± 0.07	4.1 ± 0.5	4.4

Gastric pH

The pH along the gastrointestinal tract ranges from acidic to basic and is influenced by various factors like diet, disease, presence of gases, fatty acids and other fermentation products. The gastric pH exhibits intra as well as inter subject variation. This variation in pH may significantly influence the performance of orally administered drugs. Radio telemetry measurements of the gastrointestinal pH in humans had reported that the mean value of gastric pH in fasted healthy human subjects is 1.1 ± 0.15 and in fed state is 2.0-6.

The mean gastric pH in the fed state in healthy males has been reported to be 3.6 ± 0.4 and the pH returns to basal level in about 2 to 4 hr. In women, the basal gastric pH in fasted state is slightly lower than that of the men. Gastric pH may be influenced by age, pathological conditions and drugs. About 20% of the elderly people exhibit diminished (hypochlorhydria) or no gastric acid secretion (achlorhydria) leading to basal pH value over 5.0. The pH in the proximal duodenum may rise as high as 4 pH units from stomach. This increase in the pH is caused by the bicarbonate secreted by the pancreas and the duodenal mucosa that neutralizes the acidic chyme peristalsed from the stomach. The mean pH value in fasted duodenum has been reported to be 5.8 ± 0.3 in healthy subjects while in the fasted state, small intestine has been observed to have a mean pH of 6.0 ± 0.14 . Passing from jejunum through the mid small intestine and ileum, pH rises from about 6.6 to approx. 7.5.

Floating Drug Delivery Systems (FDDS)

Floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS). these systems have a bulk density lower than gastric fluids, thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time, the drug is released slowly at a desired rate from the system. Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

- A. Effervescent System and
- B. Non-Effervescent System.

A. EFFERVESCENT SYSTEM

Effervescent systems include use of gas generating agents, carbonates(ex. Sodium bicarbonate) and other organic acid(e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide(CO₂) gas, thus reducing the density of system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

- 1) Gas Generating systems
- 2) Volatile Liquid/Vacuum Systems.

1) Gas-generating Systems

a) Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are as shown in Fig.5 and formulated by intimately mixing the CO₂ generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the great and a better control over fluctuation in plasma drug concentration.

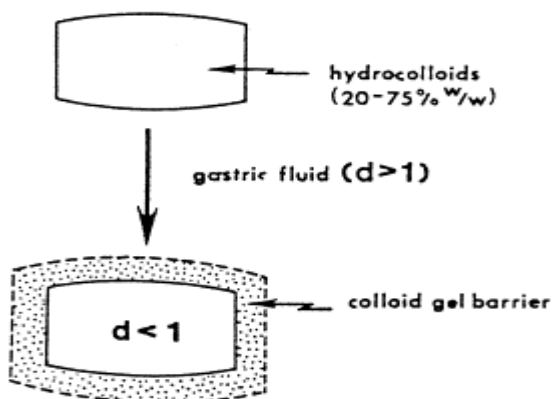


Figure 5: Intra-gastric floating tablet

2. Intra Gastric Bilayer Floating Tablets

These are also compressed tablet as shown in Fig 6 and containing two layer i.e.,

- Immediate release layer and
- Sustained release layer.

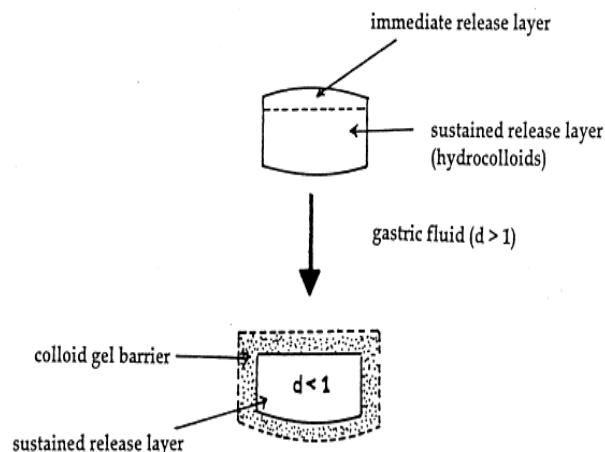


Figure 6: Intra-gastric floating bilayer tablet

3. Multiple Unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO₂ within the system.

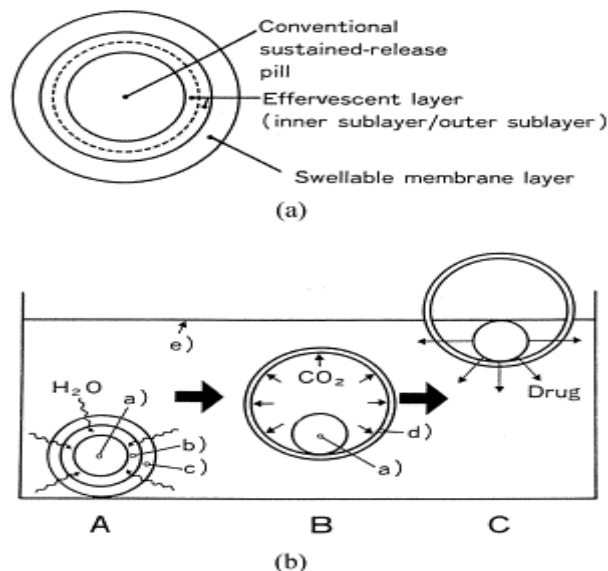


Figure 7: (a) multiple-unit oral floating dosage systems (b) Stages of floating mechanism

2) Volatile Liquid / Vacuum Containing Systems

1) Intra-gastric Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum

or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro porous compartment.

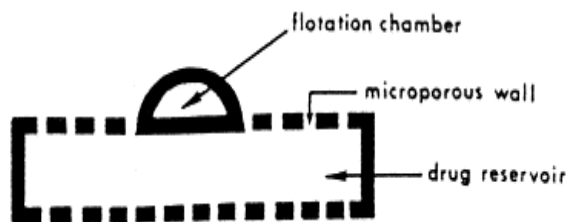


Figure 8: Intra-gastric floating drug delivery device

2) Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid.

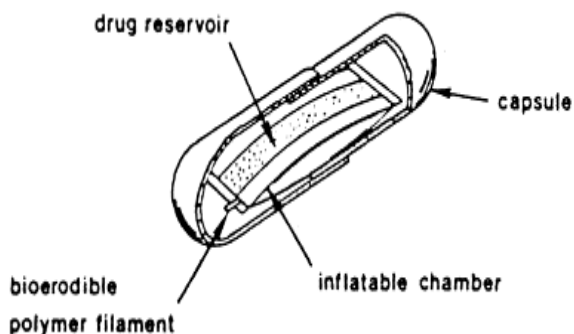


Figure 9: Gastro-inflatable drug delivery device

3. Intra-gastric Somatically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric somatically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components: drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active

compartment to dissolve the somatically salt. An osmotic pressure is then created which acts on the collapsible bag and in turn forces the bag reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bio erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

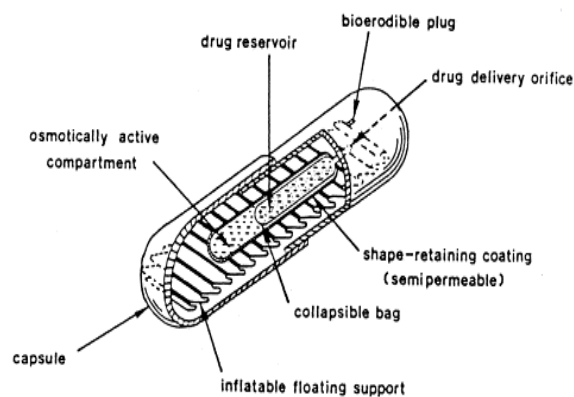


Figure 10: Intra-gastric osmotic controlled drug delivery system

B. NON EFFERVESCENT SYSTEMS

The non effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various type of this system is as follows:

1) Single Layer Floating Tablets

They are formulated by intimate mixing of drug with gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2) Bilayer Floating Tablets

A bilayer tablet contain two layer immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

3) Alginate Beads

Multi unit floating dosage forms are developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system,

which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

4) Hollow Microspheres

Hollow microspheres (Microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of drug and enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The Microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

Applications and Limitations of FDDS

FDDS systems offered several applications for drugs having poor bioavailability because of narrow absorption window in the upper part of GIT. It retained the dosage form at the site of absorption and enhanced the bioavailability.

1. Sustained drug delivery

HBS system type dosage forms remain in the stomach for several hours, increase the gastric residence time and thus release the drug over a prolonged period of time. These dosage forms have bulk density less than one, relatively large in size and did not easily pass through pylorus. Madopar HBS formulation has shown to release levodopa for up to 8 hour *in vitro*, whereas the standard formulation released levodopa in less than 30 min.

2. Site specific drug delivery

FDDS are particularly useful for drug having specific absorption from stomach or proximal part of the small intestine e.g. riboflavin, Furosemide etc. In fact, the absorption of Captopril has been found to be site specific, stomach being the major site followed by duodenum. This property prompts the development of a monolithic floating dosage form for Captopril which could prolong the gastric residence time and thus increase the bioavailability. AUC obtained with the floating tablet was approximately 1.8 times that of conventional tablets. Recently a bilayer floating capsule of misoprostol, which is a synthetic analog of prostaglandin E1, was developed and used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, the desired therapeutic levels could be achieved and wastage of drug is reduced.

3. Absorption enhancement

Drugs that have poor bioavailability because their absorption is restricted to upper GIT can be delivered specifically thereby improving their absolute bioavailability. An significant increase in the

bioavailability of floating dosage form of Captopril as compared to commercial available tablet (Acetan-25).

4. There are some cases in where the relative bioavailability of floating dosage form is reduced as compared to conventional dosage form e.g. floating tablets of amoxicillin trihydrate has bioavailability reduced to 80.5% when compared with conventional capsules. In such cases, the reduction in bioavailability is compensated by the advantages offered by FDDS e.g. patients with advanced Parkinson's disease, experienced pronounced fluctuations in symptoms while treatment with standard L-dopa. A HBS dosage form provided a better control of motor fluctuations although its bioavailability was reduced by 50-60% of the standard formulation.

5. FDDS served as an excellent drug delivery system for the eradication of *Helicobacter pylori*, which is now believed to be causative bacterium for chronic gastritis and peptic ulcers. The patients require high concentration to be maintained at the site of infection that is within the gastric mucosa. The floating dosage form by virtue of its floating ability was retained in stomach and maintained high concentration of drug in the stomach. A sustained liquid preparation of ampicillin was developed using sodium alginate that spreads out and adheres to gastric mucosal surfaces whereby releasing the drug continuously.

6. Floating system are particularly useful for acid stable drugs, drugs which are poorly soluble or unstable in intestinal fluids and for those which undergo abrupt changes in their pH-dependent solubility due to food, age and path physiological conditions of GIT. E.g. Floating system for Furosemide lead to potential treatment of Parkinson's disease. Approximate 30% drug was absorbed after oral administration.

Limitations

- 1) The floating system requires a sufficiently high level of fluid in the stomach for the system to float. This problem can be overcome by coating the dosage form with bioadhesive polymer which adhere to gastric mucosa or administering dosage form with a glass full of water (200-250 ml).
- 2) Floating system is not suitable for drugs that have stability or solubility problem in gastrointestinal fluid or that irritate gastric mucosa.
- 3) Drugs which have multiple absorption site or which undergo first pass metabolism were not desirable candidate for FDDS.
- 4) Floating dosage form should not be given to the patients just before going to the bed as gastric emptying occurs rapidly when the subject remains in supine posture.
- 5) The single unit floating dosage form is associated with "all or none concept". This problem can be overcome by formulating multiple unit system like floating microsphere or Microballoons.

6) Anti migraine drugs may interact with other medicines. When this happens, the effects of one or both of the drugs may change, or the risk of side effects may be greater. Anyone who takes these drugs should let the physician know all other medicines he or she is taking. Among the drugs that may interact with anti migraine drugs are: The single unit floating dosage form is associated with “all or none concept”. This problem can be overcome by formulating multiple unit system like floating microsphere or Micro balloons.

Factors effecting Gastric Retention

There are several factors that can affect gastric emptying of an oral dosage form which include density, size and shape of dosage form, feeding state, biological factors such as age, gender, posture, body mass index, disease state etc.

1. Effect of dosage form size & shape

Small size tablets are emptied from the stomach during the digestive phase while large size units are expelled during the house keeping waves found that floating unit with a diameter equal or less than 7.5 mm had larger gastric residence time (GRT) compared to non-floating units but the GRT was similar for floating and non-floating units having a large diameter of 9.9 mm. They found that GRT of non-floating units were much more variable and highly dependent on their size which are in the order of small < medium < large units. Moreover, in supine subjects, size influences GRT of floating and non-floating form. Tetrahedron and ring shaped devices have a better GRT as compared with other shapes.

2. Gender, posture & age

Mean ambulatory GRT in males (3.4 ± 0.6 hour) is less compared with their age and race-matched female counterparts (4.6 ± 1.2 hour) regardless of their weight, height and body surface. Women emptied their stomach at a lower rate than men even when hormonal changes due to menstrual cycle were minimized. The mean GRT in the supine state (3.4 ± 0.8 hour) was not statically significant from that in the upright, ambulatory state (3.5 ± 0.7 hour). In case of elderly, the GRT was prolonged Especially in subject more than 70 years old (mean GRT – 5.8 hour).

Table: 4 Commercially Available Floating Products

Brand name	Drug	Manufactures
Cifran O.D(tablet)	Ciprofloxacin	Ranbaxy
Liquid Gavison(liquid)	Mixture of alginates	Glaxo Smith Kline
Madopar HBS (capsule)	Levodopa and Benserazide	Roche
Glumetza(tablet)	Metformin Hydrochloride	Depomed

Anti migraine drugs

Definition

Anti migraine drugs are used to prevent or reduce the severity of migraine headaches.

3. Effect of food & specific gravity

To float FDDS in the stomach, the density of dosage form should be less than gastric content i.e. 1.0 g/cm^3 . Since, the bulk density of a dosage form is not a sole measure to describe its buoyant capabilities because the magnitude of floating strength may vary as a function of time and gradually decrease after immersing dosage form into fluid as a result of development of its hydrodynamic equilibrium. Various studies have shown the intake of food as main determinant of gastric emptying rather than food. Presence of food is the most important factor effecting GRT than buoyancy. GRT is significantly increased under fed condition since onset of MMC is delayed. Studies show that GRT for both floating and non-floating single unit are shorter in fasted subjects (less than 2 hour), but significantly prolonged after a meal (around 4 hour) shown that in the fed state, floating tablets prolonged the GRT by an average of 6 hrs than the conventional tablet while no significant difference was found in fasted state.

4. Nature of meal & frequency of food

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to fed state, to increase gastric emptying rate and prolonging the drug release. Diet rich in protein and fat can increase GRT by 4-10 hours.

5. Type of formulation

Multiple unit formulation show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profile or containing incompatible substances and permit a large margin of safety against dosage form failure compared with single unit dosage form.

6. Future Potential

- Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.
- Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.

Purpose

Migraine headaches usually cause a throbbing pain on one side of the headach Nausea, vomiting, dizziness, increased sensitivity to light and sound and other symptoms may accompany the pain. The attacks may last

for several hours or for a day or more and may come as often as several times a week. Some people who get migraine headaches have warning signals before the headaches begin, such as restlessness, tingling in an arm or leg, or seeing patterns of flashing lights. This set of signals is called an aura. The anti migraine drugs discussed in this section are meant to be taken as soon as the pain begins, to relieve the pain and other symptoms. Other types of drugs, such as anti seizure medicines, antidepressants, calcium channel blockers and beta blockers, are sometimes prescribed to prevent attacks in people with very severe or frequent migraines.

Description

Migraine is thought to be caused by electrical and chemical imbalances in certain parts of the brain. These imbalances affect the blood vessels in the brain—first tightening them up, then widening them. As the blood vessels widen, they stimulate the release of chemicals that increase sensitivity to pain and cause inflammation

and swelling. Anti migraine drugs are believed to work by correcting the imbalances and by tightening the blood vessels.

Examples of drugs in this group are ergotamine (Cafergot), naratriptan (Amerge), sumatriptan (Imitrex), rizatriptan (Maxalt), almotriptan (Axert) and zolmitriptan (Zomig). Methysergide maleate (Sansert) may be used by patients whose headaches are not controlled by other drugs, while some patients do well on other drugs. For example, combinations of ergotamine and caffeine may be very effective. The caffeine acts by constricting blood vessels to relieve the headache. Sometimes, an analgesic such as acetaminophen, caffeine and a barbiturate which acts as a sedative, are combined, as in Fioricet and similar compounds. These medicines are available only with a physician's prescription and come in several forms. Ergotamine is available as tablets and rectal suppositories; sumatriptan as tablets, injections and nasal spray; and zolmitriptan as tablets.

Table: 5 Anti migraine drugs

Anti migraine Drugs	
Brand Name (Generic Name)	Possible Common Side Effects Include:
Cafergot	Nausea, increased blood pressure, fluid retention, numbness, increased heart rate, tingling sensation
Imitrex (sumatriptan succinate)	Burning, flushing, neck pain, inflammation at injection site, sore throat, tingling sensation
Inderal (propranolol hydrochloride)	Constipation or diarrhea, headache, nausea, rash
Midrin	Dizziness, rash

Anti migraine drugs are used to treat headaches once they have started. These drugs should not be taken to prevent headaches.

Some patients are given anti-epileptic drugs, which are also known as anti convulsants, to treat migraine headaches. As of 2003, sodium valproate (Epilim) is the only anticonvulsant approved by the Food and Drug Administration (FDA) for prevention of migraine. Such newer anticonvulsants as gabapentin (Neurontin) and topiramate (Topamax) are being evaluated as migraine preventives as of early 2004.

Recommended Dosage

Recommended dosage depends on the type of drug. Typical recommended dosages for adults are given below for each type of drug.

Ergotamine

Take at the first sign of a migraine attack. Patients who get warning signals (aura) may take the drug as soon as they know a headache is coming.

TABLETS. Not more than 6 tablets for any single attack.

Not more than 10 tablets per week.

SUPPOSITORIES. Not more than 2 suppositories for any single attack.

Not more than 5 suppositories per week.

Naratriptan

Take as soon as pain or other migraine symptoms begin. Also effective if taken any time during an attack. Do not take the drug until the pain actually starts as not all auras result in a migraine.

TABLETS

Usual dose is one 1-mg tablet taken with water or other liquid.

Doses of 2.5-mg may be used, but they may cause more side effects. If the headache returns or if there is only partial response, the dose may be repeated once after 4

hours, for a maximum dose of 5 mg in a 24-hour period. Larger doses do not seem to offer any benefit.

Sumatriptan

Take as soon as pain or other migraine symptoms begin. Also effective if taken any time during an attack. Do not take the drug until the pain actually starts as not all auras result in a migraine.

Tablets: Usual dose is one 25-mg tablet, taken with water or other liquid.

Doses should be spaced at least 2 hours apart.

Anyone with liver disease should consult with a physician for proper dosing.

Injections: Not more than 6 mg per dose, injected under the skin.

Not more than two 6-mg injections per day. These doses should be taken at least 1 hour apart.

Zolmitriptan

Take as soon as symptoms begin.

TABLETS. Usual dose is 1-5 mg. Additional doses may be taken at 2-hour intervals.

Key terms

Anticonvulsant — A type of drug given to prevent seizures. Some patients with migraines can be treated effectively with an anticonvulsant.

Aura — A set of warning symptoms, such as seeing flashing lights, that some people have 10-30 minutes before a migraine attack.

Inflammation — Pain, redness, swelling, and heat that usually develop in response to injury or illness.

Status migrainosus — The medical term for an acute migraine headache that last 72 hours or longer. No more than 10 mg per 24 hour period.

General dosage advice

Always take anti migraine drugs exactly as directed. Never take larger or more frequent doses, and do not take the drug for longer than directed.

If possible, lie down and relax in a dark, quiet room for a few hours after taking the medicine.

Precautions

These drugs should be used only to treat the type of headache for which they were prescribed. Patients should not use them for other headaches, such as those caused by stress or too much alcohol, unless directed to do so by a physician. Anyone whose headache is unlike any previous headache should check with a physician before

taking these drugs. If the headache is far worse than any other, emergency medical treatment should be sought immediately. Taking too much of the anti migraine drug ergotamine (Cafergot), can lead to ergot poisoning. Symptoms include headache, muscle pain, numbness, coldness, and unusually pale fingers and toes. If not treated, the condition can lead to gangrene (tissue death).

Sumatriptan (Imitrex), naratriptan (Amerge), rizatriptan (Maxalt) and zolmitriptan (Zomig) may interact with ergotamine. These drugs should not be taken within 24 hours of taking any drug containing ergotamine.

Some anti migraine drugs work by tightening blood vessels in the brain. Because these drugs also affect blood vessels in other parts of the body, people with coronary heart disease, circulatory problems, or high blood pressure should not take these medicines unless directed to do so by their physicians.

About 40% of all migraine attacks do not respond to treatment with triptans or any other medication. If the headache lasts longer than 72 hours—a condition known as status migrainosus—the patient may be given narcotic medications to bring on sleep and stop the attack. Patients with status migrainosus are often hospitalized because they are likely to be dehydrated from severe nausea and vomiting.

Special conditions

People with certain other medical conditions or who are taking certain other medicines can have problems if they take anti migraine drugs. Before taking these drugs, be sure to let the physician know about any of these conditions:

ALLERGIES

Anyone who has had unusual reactions to ergotamine, caffeine, sumatriptan, zolmitriptan, or other anti migraine drugs in the past should let his or her physician know before taking the drugs again. The physician should also be told about any allergies to foods, dyes, preservatives, or other substances.

PREGNANCY

Women who are pregnant should not take ergotamine (Cafergot). The effects of other anti migraine drugs during pregnancy have not been well studied. Any woman who is pregnant or plans to become pregnant should let her physician know before an anti migraine drug is prescribed.

BREASTFEEDING

Some anti migraine drugs can pass into breast milk and may cause serious problems in nursing babies. Women who are breastfeeding should check with their physicians about whether to stop breastfeeding while taking the medicine.

OTHER MEDICAL CONDITIONS

Before using anti migraine drugs, people with any of these medical problems should make sure their physicians know about their conditions:

Coronary heart disease
 Angina (crushing chest pain)
 Circulatory problems or blood vessel disease
 High blood pressure
 Liver problems
 Kidney problems
 Any infection
 Eye problems.

USE OF CERTAIN MEDICINES

Taking anti migraine drugs certain other drugs may affect the way the drugs work or may increase the chance of side effects.

Side effects

The most common side effects are fluid retention, flushing; high blood pressure; unusually fast or slow heart rate; numbness; tingling; itching; nausea; vomiting; weakness; neck or jaw pain and stiffness; feelings of tightness, heaviness, warmth, or coldness; sore throat; and discomfort of the mouth and tongue.

More serious side effects are not common, but they may occur. If any of the following side effects occur, call a physician immediately:

- Tightness in the chest
- Bluish tinge to the skin
- Cold arms and legs
- Signs of gangrene, such as coldness, dryness, and a shriveled or black appearance of a body part
- Dizziness
- Drowsiness
- Shortness of breath or wheezing
- Skin rash
- Swelling of the eyelids or face.

Possible side effects with anticonvulsants include dizziness, drowsiness, emotional upset, skin rash, temporary hair loss, nausea and irregular menstrual periods.

Other side effects may occur with any anti migraine drug. Anyone who has unusual symptoms after taking this medicine should get in touch with his or her physician.

Alternative treatments

There are two herbal remedies that are reported to be effective as alternative treatments for migraine. One is feverfew (*Tanacetum parthenium*), an herb related to the daisy that is traditionally used in England to prevent migraines. Published studies indicate that feverfew can reduce the frequency and intensity of migraines. It does not, however, relieve pain once the headache has begun. The other herbal remedy is butterbur root (*Petasites hybridus*). Petadolex is a natural preparation made from

butterbur root that has been sold in Germany since the 1970s as a migraine preventive. Petadolex has been available in the United States since December 1998.

Interactions

- Beta blockers such as atenolol (Tenormin) and propranolol (Inderal)
- Drugs that tighten blood vessels such as epinephrine (EpiPen) and pseudoephedrine (Sudafed)
- Nicotine such as cigarettes or Nicoderm, Habitrol and other smoking-cessation drugs
- Certain antibiotics, such as erythromycin and clarithromycin (Biaxin)
- Monoamine oxidase inhibitors such as phenelzine (Nardil) and tranylcypromine (Parnate)
- Certain antidepressants, such as sertraline (Zoloft), fluoxetine (Prozac) and paroxetine (Paxil)
- Fluvoxamine (Luvox), prescribed for obsessive compulsive disorder or chronic pain.

Anticonvulsants should not be taken together with aspirin, alcohol, or tranquilizers.

Remember naratriptan, sumatriptan, rizatriptan and zolmitriptan may interact with ergotamine. These drugs should not be taken within 24 hours of taking any drug containing ergotamine.

PLAN OF WORK

A. Quantification of the drug

1. Construction of the standard curve
2. Analytical method validation
3. Drug-excipients interaction studies

B. Formulation of floating Sumatriptan succinate tablets

C. Evaluation of floating Sumatriptan succinate tablets

a. Physical Parameters

1. Tablet hardness, Uniformity of weight, Tablet friability
2. Assay

b. In vitro studies

1. *In vitro* buoyancy test
2. *In vitro* dissolution studies
3. Interpretation of dissolution data

ANALYTICAL METHOD AND ITS VALIDATION

Estimation of Sumatriptan succinate

A UV spectrophotometric method based on measurement of absorbance at 227nm in 0.1N HCL was used for the estimation of Sumatriptan succinate.

Materials

- 1) Sumatriptan succinate
- 2) 2g NaCl
- 3) 7 ml HCl

Preparation of 0.1 N HCl: 2g of NaCl and 7 ml of concentrated HCl was diluted with 1000 ml of distilled water to get 0.1 N HCl.

Scanning

For UV scanning for λ_{max} of Sumatriptan succinate, about 100 mg of pure drug was weighed and transferred to a 100ml volumetric flask. 0.1 N HCl solution was added and mixed well. Then 1 ml of this solution was diluted to 100ml with 0.1 N HCl in a volumetric flask to obtain a solution of 10 μ g/ml and scanned for λ_{max} within the range of 200-400. It was found to be 227nm.

Procedure

100 mg of Sumatriptan succinate was accurately weighed and transferred to a 100ml volumetric flask. Few ml of 0.1 N HCl was added and mixed well to dissolve the drug. Finally the volume was made upto 100 ml with 0.1N HCl. It results in a concentration of 1000 μ g/ml. Then 10 ml of this solution was transferred to another 100ml volumetric flask and diluted to obtain a solution of 100 μ g/ml concentration. From this 0.2, 0.4, 0.6, 0.8, 10ml of the solutions were taken and diluted up to 10ml in 10ml volumetric flasks which results in 2, 4, 6, 8, 10 μ g/ml concentrations respectively. The absorbance values were measured using double beam U.V. spectrophotometer at a λ_{max} of 227 nm. The absorbance values were plotted against concentration (μ g/ml) to obtain the standard curve.

Validation of the method

The method was validated for linearity, accuracy, precision and interference by other materials used in the

present study. Accuracy and precision (reproducibility) of the method was studied by analyzing six individual weighed samples of sumatriptan succinate. Interference by the other materials was evaluated by preparing and analyzing the samples by the proposed method.

Drug –Polymer Compatibility Studies by FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). combination of drug and polymers were shows no significant interaction between Sumatriptan succinate and polymer.

Formulation Sumatriptansuccinate floating tablets

Sumatriptansuccinate was used with HPMC K4M, Gurgum are polymers in varying ratios to formulate the floating tablets. Micro crystalline cellulose (MCC) was used as a diluents, sodium bicarbonate was incorporate on gas generating agents, Magnesium stearate was used as a lubricant and talc was used as a glidant. The tablet weight was adjusted to contain 100 mg of in each Sumatriptansuccinate tablet.

The floating tablets were prepared by mixing drug, HPMC, Gurgum, Mcc Magnesium stearate and talc geometrically in a mortar and pestle to get a uniform mixture. The mixture was passed through sieve no 40 and adds granulating agent obtaining granules by using sieve no25 and dried at 40^oc 20-30min. add talc and Magnesium stearate was added and directly compressed using a tablet compression machine fitted with 9 mm flat punches. The tablet weight was adjusted to 250 mg and 50 tablets for each formula were prepared.

Table 6: Formulae for Sumatriptansuccinate floating tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7
Samaritan succinate	100	100	100	100	100	100	100
HPMCK4M	25	0	50	0	65	0	32.5
Gurgum	0	25	0	50	0	65	32.5
Sodium bicarbonate	50	50	50	50	50	50	50
MCC	65	65	40	40	25	25	25
Magnesium stearate	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5
Total	250	250	250	250	250	250	250

* All quantities are in mg

EVALUATION OF TABLETS

I) Pre-compression parameters

a) Determination of initial bulk density and final bulk density

20 gm of the powder (W) was weighed and carefully poured into 20 ml measuring cylinder and the initial volume (V_0) was measured. Then the measuring cylinder was set into the density determination apparatus (bulk density apparatus, electro lab). The density apparatus was set for 100 taps and after that the final volume (V_f) was measured and continued operation till the two consecutive readings were equal.

b) Compressibility index

The *Compressibility index* and *Hausner ratio* are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the *Compressibility Index* and the *Hausner Ratio*.

The compressibility index and Hausner ratio were calculated using measured values for bulk density (D_b) and tapped density (D_t) as follows:

$$\text{Compressibility index} = \frac{D_t - D_b}{D_b} \times 100$$

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

c) Angle of repose

The flow characteristics were measured by angle of repose method. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan \theta = \frac{h}{r}$$

$$\theta = \tan^{-1} \frac{h}{r}$$

Where h = height of pile

r = radius of the base of the pile

θ = angle of repose

II) Post-compression parameters

a) Tablet thickness

The thickness in millimeters (mm) was measured individually for 10 tablets by using vernier calipers. The average thickness and standard deviation were reported.

b) Tablet Hardness

The crushing strength Kg/cm^2 of prepared tablets was determined for 6 tablets of each formula by using Monsanto tablet hardness tester. The average hardness and standard deviation values were tabulated.

c) Friability

Twenty tablets were weighed and placed in the friabilator and apparatus was rotated at 25 rpm for 4 minutes. After 100 revolutions the tablets were deducted and weighed again. The percentage friability was measured using the formula.

$$\%F = \left\{ 1 - \frac{W_t}{W} \right\} \times 100$$

Where, % F = friability in percentage

W = Initial weight of tablet

W_t = weight of tablets after revolution

d) Weight variation

Twenty tablets from each batch were individually weighed using an analytical balance. The average weight and standard deviation were calculated and the results were reported.

e) Drug content

250 mg of the powdered tablet material equivalent to 10 mg of sumatriptansuccinate was taken and transferred into 100 ml volumetric flask. Then 30 ml of 0.1N HCL was slowly added mixed properly and the volume was made upto 100 ml with 0.1N HCL. The above solution was filtered and 10 ml of filtrate was taken into 100 ml volumetric flask and made upto final volume with 0.1N HCL and the drug content was estimated by measuring the absorbance at λ_{max} 227 nm using a spectrophotometer.

III) In Vitro Buoyancy Test

The prepared tablets were subjected to *in vitro* buoyancy test by placing them in 250 ml beaker containing 200 ml of 0.1 N HCl (pH 1.2, temp. $37 \pm 0.5^\circ\text{C}$). The time between introduction of the dosage form and its buoyancy in the medium and the floating durations of tablets was calculated for the determination of lag time and total buoyancy time by visual observation. The Time taken for dosage form to emerge on surface of medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Determination of Swelling Index

The swelling index of tablets was determined in 0.1N HCL (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 h. The swelling index, expressed as a percentage, and was calculated from the following Equation.

Weight of tablet at time (t) – Initial Weight of tablet \times 100

$$\text{SI} = \frac{\text{Weight of tablet at time } (t) - \text{Initial Weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

IV) Dissolution Protocol

In Vitro dissolution study was carried out using Electro lab dissolution tester using type II USP apparatus using 500 ml of 0.1 N HCl (pH 1.2) for 10 hours. The temperature of the dissolution medium was kept at $37 \pm 0.5^\circ\text{C}$ and the paddle was set at 75 rpm. 5 ml of sample solution was withdrawn at specified interval of time and filtered through what man filter paper. 5ml of 0.1N HCl was added into the baskets to maintain the constant volume. The absorbance of the withdrawn samples was measured at λ_{max} 227 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of sumatriptansuccinate prepared in 0.1N HCl (pH 1.2) at λ_{max} 227 nm.

V) Similarity Factor (f_2)³

Similarity factor f_2 was calculated using following formula:

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n [(R_t - T_t)^2]^{-0.5} \times 100 \right] \right\}$$

n = number of dissolution time points

R_t =dissolution value of reference drug product at time t

T_t =dissolution value of the test drug product at time t

The guidelines for interpretation of Similarity factor are:

100- Dissolution profiles are identical

≥ 50 - Similarity or equivalence of two profiles

VI) Modelling of Dissolution Profiles

In vitro dissolution has been recognized as an important element in drug development and assessment of Bioequivalence. Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of 't' (time) related to the amount of drug dissolved from the pharmaceutical dosage system.

Whenever a new solid dosage form is developed or produced, the drug release/dissolution from solid pharmaceutical dosage form is necessary to ensure that the drug dissolution occurs in an appropriate manner.

In the present study, data of the *in vitro* release were fitted to different equations and kinetic models to explain the release kinetics of sumatriptansuccinate from the floating tablets. The kinetic models used were a Zero order equation, First order, Higuchi equation and Korsmeyer-Peppas models.

VI) Zero Order Kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation;

$$Q_t = Q_0 + K_0 t$$

Where, Q_t = amount of drug released in time 't', Q_0 = initial amount of drug in the solution, k_0 = zero order release constant.

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage form, as in the case of some transdermal system, as well as matrix tablets with low soluble drugs coated form, osmotic systems, etc.

VII) First Order Kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman. The following relation can express this model:

$$\log Q_t = \log Q_0 + \frac{k_1 t}{2.303}$$

Where, Q_t = amount of drug released in time 't', Q_0 = initial amount of drug in the solution, k_1 = first order release constant.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

VIII) Higuchi Model

Higuchi developed several theoretical models to study the release of water soluble drugs incorporated in semisolid and/or solid matrixes. Simplified Higuchi model can be expressed by following equation:

$$Ft = k_H t^{\frac{1}{2}}$$

Where, k_H = Higuchi diffusion constant, f_t = fraction of drug dissolved in time 't'.

Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

IX) Korsmeyer-Peppas Model: Korsmeyer developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (t);

$Ft = at^n$ Where, a = constant incorporating structural and geometric characteristics of the drug dosage form, n = release exponent, $f_t = M_t/M_\infty$ = fraction of drug released.

This model is generally used to analyze the release of pharmaceutical polymeric dosage forms where the release mechanism is not well known or where more than one type of release phenomena could be involved.

X) Stability studies

Adequate stability data of drug and its dosage form is essential to ensure the strength safety, identity, quality purity and *in-vitro* release rate that they claim to have at time of use. Sustained release product should release predetermined amount of drug at specified time intervals, which should not change on storage. Any considerable deviation from sustained release would render release product useless.

Stability is defined as "the capacity of drug product to remain within specification established to ensure its identity, strength, quality and purity". The purpose of stability study is not only to characterize the degradation of drug product but also to establish expiration dating period or shelf-life applicable to all future batches of drug product.

Stability studies are of three types:

1. Long term stability studies
2. Intermediate stability studies

3. Accelerated stability studies

Accelerated stability studies are useful in following ways:

1. The result provide estimate of kinetic parameters for the rate of reaction.
2. The results can be used to characterize the relationship between degradation and storage condition.
3. The results provide critical information on design and analysis of long-term stability studies under ambient conditions at the planning stage.

Developed tablet formulations were wrapped in aluminium foils individually and placed in stability chamber. Conditions were set at 40°C, 75% RH, room temperature (25°C, 60% RH) and 2-8°C as per ICH guidelines. Stability studies were carried out for three months. Samples were withdrawn at an interval of 1, 2 and 3 months, analyzed for *in-vitro* dissolution.

DISCUSSION

Discussion of calibration

The method obeyed Beer's law in the concentration range of 0-25 µg/ml. low RSD values in Table 9 ensured reproducibility of the method. Recovery of the sumatriptan succinate from the physical mixture of drug and PHP was found to be 99.5%. Thus the method was found to be suitable for the estimation of sumatriptan succinate contents in various products and *in vitro* dissolution studies in the present study.

Formulations

Sumatriptan succinate is stable in acidic medium, when orally administered about 15% of the normal dose is absorbed. So it fulfills the required criteria for selection of the drug under floating drug delivery systems. The aim of the present work is to develop Gastroretentive floating tablets of sumatriptan succinate using Natural and semi synthetic polymers and excipients. The formulation method based on effervescent components at fixed preparations in all formulations. sodium bicarbonate were used as effervescent components at fixed preparations in all the formulations.

Floating behavior (F5) best formulation



Initially

Each tablet contains 100 mg of Sumatriptan succinate and the total weight of the tablets was adjusted to 250 mg. Micro crystalline cellulose using as the diluent. HPMC (K4M) (synthetic), Gurgum (natural) was used as a swellable drug release retardant polymer at various proportions. The function of talc and magnesium stearate was glidant and lubricant respectively and used at in all the formulations.

The powder blend showed the Angle of repose values which ranges from 37.89±0.01 to 34.89±0.02 indicates passable and good flow property. The Compressibility index value which ranges from 15.9±0.02 to 21.81±0.01 indicates good flow property. Hausner ratio values which ranges from 1.1±0.01 to 1.19±0.01 indicates fair to passable flow property.

The drug content values ranges from 98.52±0.07 to 92.68±0.55. Hardness values ranges from 5.1±0.18 to 6.1±0.36. and Friability ranges are 0.20±0.10 to 0.40±0.05. The weight variation results of average tablet weight and percentage variation were present in the range of 248.0 ±0.09 to 251.0±0.21.

Floating behaviour

IN VITRO STUDIES

IN VITRO BUOYANCY

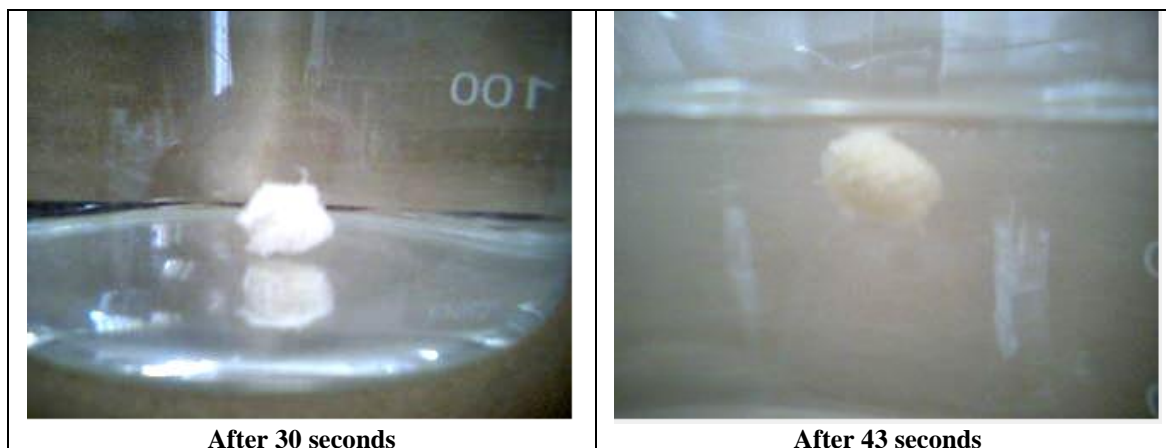
In vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

Table no. 7: *In Vitro* buoyancy

S.No	F. Code	<i>In vitro</i> buoyancy (h)
1	F1	8
2	F2	>7
3	F3	8
4	F4	9
5	F5	10
6	F6	>8
7	F7	9

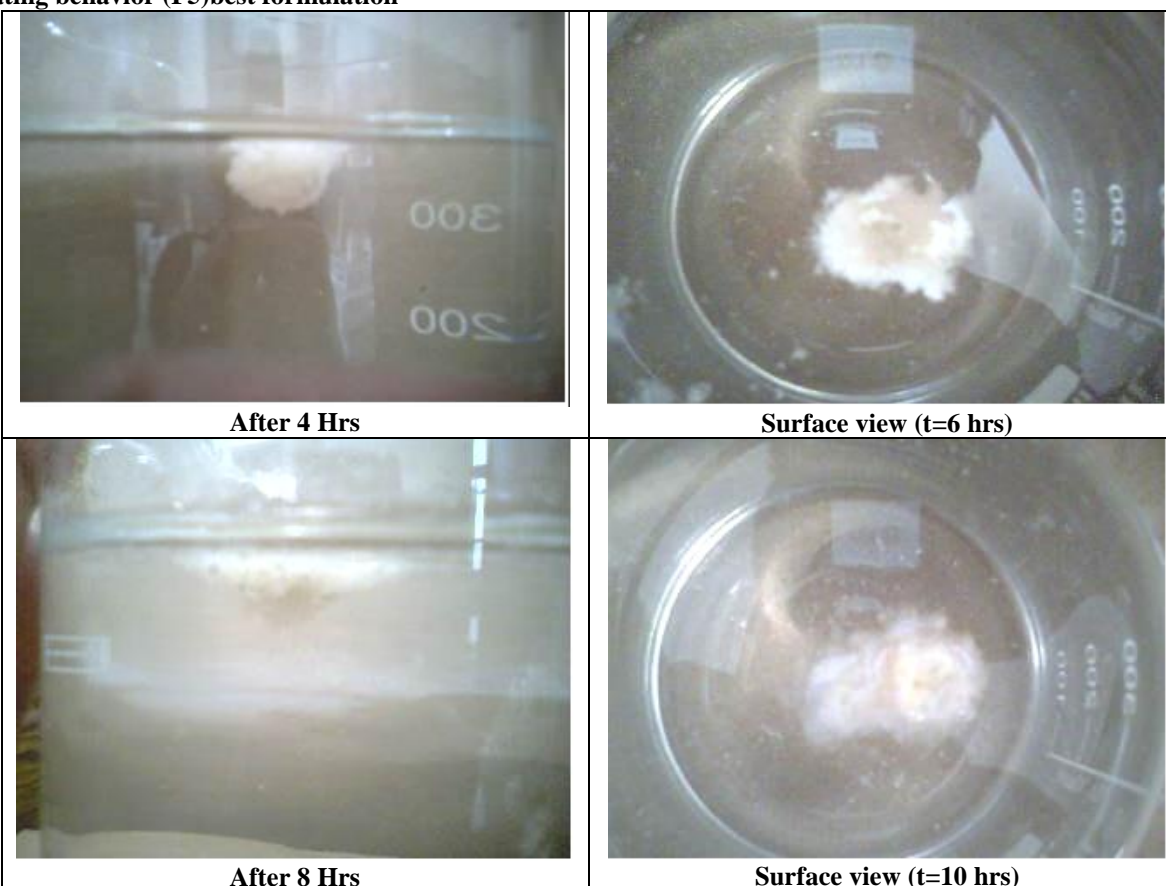


After 15 seconds



After 30 seconds

After 43 seconds

Floating behavior (F5)best formulation

After 4 Hrs

Surface view (t=6 hrs)

After 8 Hrs

Surface view (t=10 hrs)

In Vitro Buoyancy Study of Sumatriptan succinate Floating Tablets.**IN VITRO DRUG RELEASE STUDIES**

The release rate of floating tablets was determined using United States Pharmacopeia Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCL, at $37 \pm 0.5^\circ\text{C}$ and 75 rpm. A sample (5 mL) of the solution was withdrawn at 1,2,4,6,8,10 up to 10hrs. and the samples were replaced with fresh dissolution medium. The samples were filtered. Through a 0.45μ membrane filters and diluted to a suitable concentration with 0.1N HCL. Absorbance of these solutions was measured using a UV- spectrophotometer.

Dissolution profiles

The effect of swellable retardant polymers are like HPMC K4M, Gurgum and Sodium bi carbonate is used as a gas generating agents. MCC is diluents and Talc & magnesium stearate was glidant and lubricant and drug release was studied and the data was reported in the corresponding tables and graphs in the formulations.

In case of F1(5%) total amount of drug was released within 4hrs. it may be low proportion of the polymer and high preparation of wet granulation diluents MCC. hence in the.

Next formulation the proportion of Gurgum(5%) was using instead of HPMCK4m. The amount of drug release showed increased manner with in 6 hrs compared to F1 formulation. In this formulation did not maintained sustained release throughout period.

In F3 formulation was using HPMCK4m (10%) polymer and the release rate increased manner i.e 99% of the drug was released within 6 hrs.

In F4 Guargum (10%) formulation The modification in the subsequent formulations released rate may be retard 99.3% of the drug was released slowly with in 8hrs. Was the release retarding polymer and as its concentration was increased and the amount of drug release also increased. The release did not maintain in through out of period.

In F5 formulation may be using HPMCK4m (20%) achieved sustained release rate but they of the drug 99.3% of the drug was released slowly over 10hrs time period. And release may be maintained sustained release so this is the best fit to compared other formulations.

In F6 formulation may be using Guargum (20%) The optimum concentration of Gurgum retarding polymer and as its concentration was increased the release rate was 92.9% of the drug released within 10hrs.

In F7 formulation may be using combination HPMCK4m+Guargum (20%) and the amount of drug release less i.e only 82% of drug released within 10hrs.

However the hardness of F5,F6 was Found to be slightly less compared to other formulations.

F5 formulations showed floating lag time of 69sec and 99% of drug release over 10hrs period it was found to be the best formulation.

The floating lag times in table-no were found to be higher in the F7 formulation. The floating time in table no were found to be higher in the F3 Formulation. The drug release kinetic and mechanism were studied by fitting the data in to various models.

The drug release kinetics and mechanism were studied by fitting the data into various models. The R^2 values for each kinetic model i.e. zero order, first order and Higuchi and Korsmeyer peppas were shown in Table-20. The release kinetics in case of some of the formulations followed kinetics like F1,F2, F4 follows first order and except preparations follows F3,F5,F6,F7 Zero order F1,F4,F3,F5,F6,F7 diffusion controlled mechanism as the R^2 values were closed to one in Higuchi model.

Drug release kinetics of the best formulation is F5 corresponds best to peppas's model and release mechanism as per n value (n=0.4688) appears to be non-fickian (anomalous)diffusion.

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SUMMARY

Gastroretentive floating tablets of Sumatriptan succinate were successfully prepared with hydrophilic polymers like HPMC K4M, Guar gum, From the compatibility studies for drug and excipients it was observed that there was no interaction between drug and excipients.

The formulated batches were evaluated for Preformulation studies that are Angle of repose, Carr's index and Hausner's ratio batches complied with the pharmacopoeial specifications.

The formulated batches were evaluated for physicochemical parameters like hardness, thickness, weight variation, friability, drug content, floating lag time and swelling index. The physical properties like hardness, thickness, weight variation and friability of all batches complied with the pharmacopoeial specifications. The drug content of all tablets was in the range of 92.68 - 98.52±0.07%. Floating properties from the evaluation results it was observed that the tablets containing Sodium bi carbonate and HPMC K4M (100+60 mg) F5 showed greater floating lag time and when compared to other prepared formulation. Swelling index of floating tablets showed significant differences in their swelling index.

All batches showed *in-vitro* buoyancy greater than 10 hrs. From the *in vitro* dissolution analysis it was found that the batches containing HPMC K4M and F5 showed greater drug release than other batches. It was observed that the increasing concentration of HPMC had a

retarding effect on the drug release from the polymer matrices.

CONCLUSION

The Effervescent-based floating drug delivery is a promising approach to achieve in vitro buoyancy by using gel forming polymer HPMCK4M, Natural polymer Guar gum and the floating tablets were prepared by using wet granulation technique. The floating tablets of Sumatriptan succinate were evaluated for physicochemical characteristics like thickness, hardness, weight variation, friability, drug content, floating lag time and swelling index. The *in-vitro* buoyancy studies, *in-vitro* drug release studies,

The result obtained is encouraging, because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in the floating dosage forms. Hence Sumatriptan succinate floating tablets could be promising one as they, improve bioavailability, minimize the dose and reduces the side effects.

Based on this work it was found that floating type of effervescent drug delivery systems holds a lot of potential and comparable with effervescent systems. We can certainly explore this drug delivery with many other existing drugs. It is the responsibility of future scientists working in this area to effectively use the potential of this drug delivery system for the benefit of mankind.

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