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RAFT FORMING TABLETS: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

In this article, a novel drug delivery system of GRDDS (Gastro retentive Drug Delivery System) named as Raft forming tablet is discussed. Drugs with narrow absorption window in the gastrointestinal tract have poor absorption. Therefore, gastro retentive drug delivery systems (GRDDS) have been developed, which prolong the gastric emptying time. Several techniques such as Rafting drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, super porous hydrogels and magnetic systems, have been employed. The Rafting drug delivery systems are useful approach to avoid this variability with increase the retention time of the drug delivery systems for more than 12 hours. Raft forming tablets are those forms which forms a gel like structure in presence of acidic environment of stomach which is known as Raft. So by this way numerous advantages and application are done by means of same dosage form.

KEYWORDS: GRDDS, Gel Formation tablets, Rafting tablets, Novel Drug, Gastro retentive Drug Delivery System.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. The high level of patient compliance in taking oral dosage forms is due to the ease of administration, patient compliance, flexibility in formulation and handling of these forms.[1] However the oral route of administration suffers with certain drawbacks mainly short residence time of the dosage form in the GI tract, unpredictable gastric emptying and degradation of the drug due to highly reactive nature of GI contents. Gastric emptying is a complex process and makes *in vivo* performance of the drug delivery

system uncertain. Formulation of Rafting drug delivery systems is a useful approach to avoid this variability with increased gastric retention time of the drug delivery system.[2] A systems or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time .While the system is rafting on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach .This results in an increased gastric residence time and a better control of the fluctuation in plasma drug concentration.

Drug delivery systems are used for maximizing therapeutic index of the drug and also for reduction in the side effects. The most preferred route is the oral route especially for the administration of therapeutic drugs because low cost of therapy and ease of administration leads to higher level of patient compliance. More than 50% of the drug delivery systems available are to be administered through oral route. Reasons behind using oral route are that it is the most promising route of the drug delivery and effective oral drug delivery may depend upon many factors such as gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form and site of absorption of drug. High level of patient compliance is the major advantage of using the oral route.

To modify the GI transit time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes to 2 hours.

Gastro retentive 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.[3]

It has applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and patients are highly benefited. Controlled release drug delivery systems that retain in the stomach for a long time have many advantages over sustained release formulations.

Such retention systems (i.e. GRDDS) are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. Gastric retention may increase solubility for the drugs which are poorly soluble in intestine due to alkaline pH before they are emptied, resulting in improved bioavailability.

These systems also offer advantages in improving GIT absorption of a drug with narrow absorption windows as well as for controlling release of those drugs which are having site-specific absorption limitations.[4]

These systems are useful in case of those drugs which are best absorbed in stomach for eg. Albuterol. From the formulation and technological point of view, rafting drug delivery system (GRDDS) is considerably easy and logical approach in development of GRDFs. Therefore, this review article focuses on the current technological development in GRDDS with special emphasis on the principal mechanism of floatation and advantages to achieve gastric retention and its potential for oral controlled drug).

ANATOMY OF THE GASTROINTESTINAL TRACT[5]

The gastrointestinal tract can be divided into three main regions namely

1. Stomach
2. Small intestine- Duodenum, Jejunum and Ileum
3. Large intestine

The GIT is a continuous muscular tube, extending from the mouth to the anus, which functions to take in nutrients and eliminate waste by such physiological processes as secretion, motility, digestion, absorption and excretion. The organization of the GIT, from stomach to large intestine, is shown in Fig.1. The stomach is a J shaped enlargement of the GIT which can be divided into four anatomical regions: cardia, fundus, body and antrum. The main function of the stomach is to store and mix food with gastric secretions before emptying its load (chyme) through the pyloric sphincter and into the small intestine at a controlled rate suitable for digestion and absorption. When empty, the stomach occupies a volume of about 50 ml, but this may increase to as much as 1 liter when full.

The walls of the GIT, from stomach to large intestine, have the same basic arrangement of tissues, the different layers, from outside to inside, comprising serosa, longitudinal muscle, intermuscular plane, circular muscle, submucosa, muscular is mucosae, lamina propria and

epithelium. In addition to longitudinal and circular muscle, the stomach has a third muscle layer known as the "oblique muscle layer", which is situated in the proximal stomach, branching over the fundus and higher regions of the gastric body. The different smooth muscle layers are responsible for performing the motor functions of the GIT, i.e. gastric emptying and intestinal transit.

MUCUS: STRUCTURE, FUNCTION AND COMPOSITION

Mucus is a complex viscous adherent secretion which is synthesized by specialized goblet cells. These goblet cells are glandular columnar epithelium cells and line all organs that are exposed to the external environment. Mucus is found to serve many functions within these locations such as lubrication for the passage of objects, maintenance of a hydrated epithelium layer, a barrier function with regard to pathogens and noxious substances and as a permeable gel layer allowing for the exchange of gases and nutrients to and from underlying epithelium.

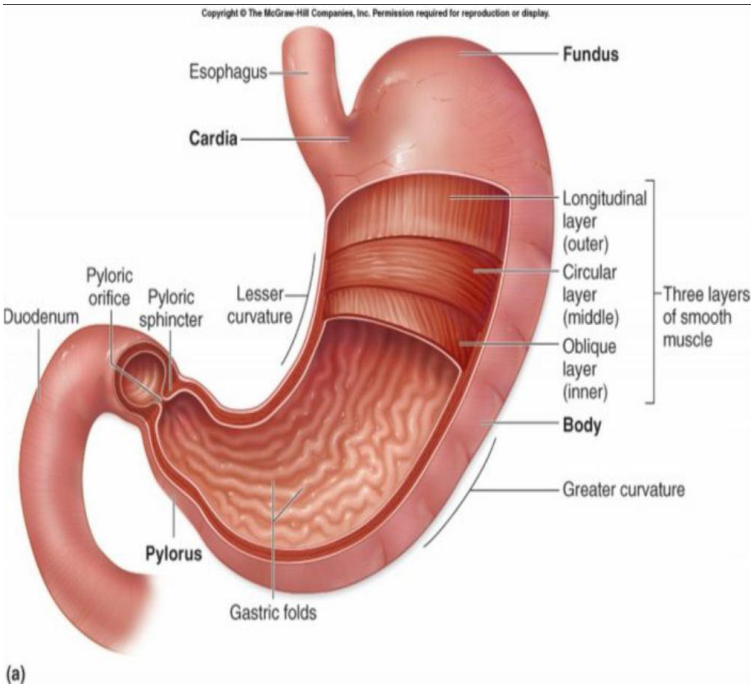

Figure 1: Anatomy of the gastrointestinal tract

From an engineering point of view, mucus is an outstanding water-based lubricant whose properties are extensively exploited within nature. Mucus is composed mainly of water (>95%) and mucin, which are glycoprotein's of exceptionally high molecular weight (2–14 X106 g/mol). Also found within this ''viscoelastic soup" are proteins, lipids and mucopolysaccharides, which are found in smaller proportions (<1%). The mucin glycoprotein's form a highly entangled network of macromolecules that associate with one

another through non covalent bonds. Such molecular association is central to the structure of mucus and is responsible for its rheological properties. Furthermore, pendant sialic acid (pKa = 2.6) and sulphate groups located on the glycoprotein molecules result in mucin behaving as an anionic polyelectrolyte at neutral pH. Other nonmucin components of mucus include secretory IgA, lysozyme, lactoferrin, lipids, polysaccharides, and various other ionic species. Some of these non-mucin components are believed to be responsible for the bacteriostatic action observed in mucus**.**

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Anatomically the stomach is divided into 3 regions:

- Fundus,
- Body, and
- Antrum pylorus.

The proximal part 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. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases.

1. Phase I (basal phase)
2. Phase II (preburst phase)
3. Phase III (burst phase)
4. Phase IV

Table1: Four phases in migrating myoelectric complex (MMC)

Phase I	It is a quiescent period lasting from 30 to 60 minutes with no contractions.
Phase II	It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.
Phase III	This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also known as ''house-keeper wave,'' sweep gastric contents down the small Intestine
Phase IV	This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I.

Phase l: (basal phase) Period of no contraction

Phase ll: (preburst phase) Period of intermittent contraction

Phase lll: (burst phase) Period of regular contraction at the maximal frequency that migrate distally.

Phase lV: Period of transition between phase lll and phase l after the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase 2 of fasted state. These contractions result in reducing the size f food particles (to less than 1 mm), which are propelled towards the pylorus in a suspension from. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.Scintigraphic studies determining gastric emptying rate revealed that orally administered controlled released dosage forms are subjected to complications that of short gastric residence time and unpredictable gastric emptying rate.

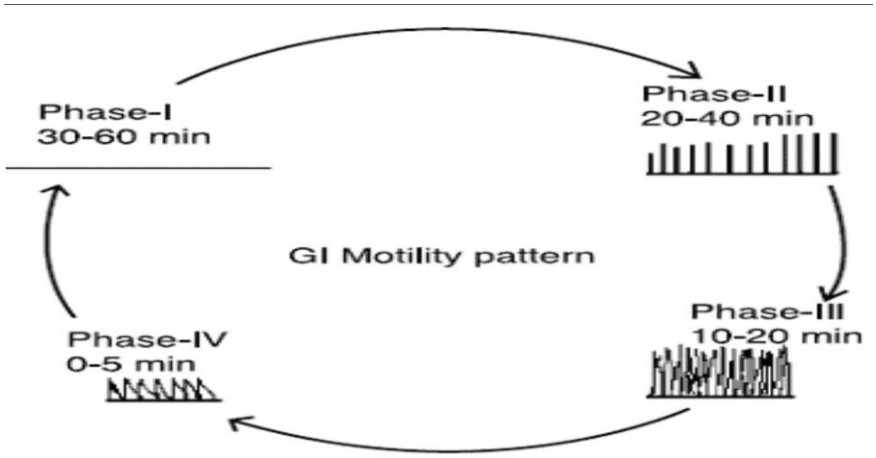

Figure 2: A simplified schematic representation of the interdigestive motility pattern, frequency of contraction forces during each phase, and average time Period for each period.

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF GRDDS[6]

Gastric retention time (GRT) is depends upon the dosage form buoyancy which is further dependent on the density. Density of the dosage form that is used for GRDDS should be less than the gastric contents (1.004gm/ml).

Size and Shape

Dosage form unit with a diameter of more than 7.5 mm are more suitable candidate as compared to those which have a diameter of 9.9 mm because they have an increased GRT. Similarly the dosage form having a tetrahedron shape and ring shape devises with a flexural

modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100% retention and hence more suitable for GRDDS as compared with other shapes.

Viscosity of polymer

Viscosity of polymer and their interaction greatly affect the drug release and rafting properties of GRDDS. Low viscosity polymers (e.g., HPMC K100LV) were found to be more suitable candidates for GRDDS than high viscosity polymers (e.g., HPMC K4M) because they improve rafting properties. Also, with an increase in polymer viscosity a decrease in the release rate was observed.

Fed or Unfed State

Under fasting conditions, the GRT of the unit is expected to be very short because of the periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5to 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 then obviously GRT of the dosage form expected to be very short. But, in the fed state, GRT is considerably longer because MMC is delayed.

Nature of meal

Motility pattern of the stomach can change to fed state when indigestible polymers or fatty acid salts are fed and because of this the gastric emptying rate is decreased and drug release is prolonged.

Frequency of feed

When successive meals are given, the GRT can increase by over 40 minutes compared with a single meal because of the low frequency of MMC.

Gender

Mean GRT of a male in meals (3.4±0.4 hours) is less compared to the female of the same age and race (4.6±1.2 ours), regardless of the height, weight, and body surface of the two.

Age

Elderly people have a significantly longer GRT, especially those who are over 70 years of age.

Posture

Rafting forms are protected by an upright position against postprandial emptying because at this position, the rafting form remains above the gastric contents irrespective of its size. While the conventional dosage form sink to the lower part of the distal stomach at this position from where they are expelled by antral peristaltic movements through the pylorus. But supine position offers no such protection against early and erratic emptying of rafting dosage forms.

Only large dosage forms (both conventional and rafting) experience prolonged retention when they are anywhere between the lesser and greater curvature of the stomach. On moving distally, these units show significant reduction in GRT compared with upright subjects because of peristaltic movement.

Need for GRDDS

- ✓ Conventional oral delivery is widely used in pharmaceutical field to treat diseases. However, conventional delivery had many drawbacks and major draw-back is non-site specificity.
- ✓ Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site.
- ✓ Pharmaceutical field is now focusing towards such drugs which require site specificity.
- ✓ Gastro-retentive delivery is one of the site specific delivery for the delivery of drugs either at stomach or at intestine. It is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine.

ADVANTAGES OF RAFTING DRUG DELIVERY SYSTEM[7]

Sustained drug delivery

Rafting drug dosage forms can remains in the stomach for prolong time and enhance the GRT of numerous drugs. Also, these dosage forms are large in size due to which don't pass through pylorus (0.9-1.9 cm opening). So, GRDDS provides sustained drug delivery.

Site-specific drug delivery

Some drugs such as furosemide, riboflavin show site specific absorption site in the upper part of GIT. In fact, the major site of absorption is stomach for furosemide, followed by the

duodenum. So, Rafting dosage form of furosemide can be beneficial to prolong the GRT, hence it increases the bioavailability.

Local action in stomach

The GRDDS are beneficial for drugs that are desire to produce local action in the stomach. For example: antacids.

Reduce irritation of acidic drugs

Acidic drugs, after administration may cause irritation on the stomach wall. Hence Rafting dosage forms may be advantageous for the administration of acidic drugs such as aspirin and other.

Advantageous to drugs which are unstable in intestine environment

Drugs such as captopril, ranitidine HCl, metronidazole which are unstable in the intestinal or colonic environment can be administered by making Rafting dosage forms.

Beneficial to drugs that show low solubility at high pH

Some drugs such as diazepam, chlordiazepoxide, and verapamil show low solubility at high pH. GRDDS can be useful because it enhance the GRT of these drugs and hence increase the bioavailability of these drugs by increasing absorption.

Pharmacokinetic advantages

GRDDS maintain constant blood level because of sustain released nature of these dosage forms, easy in administration and patient compliance is also improved.

Apart from above, few merits are as follow:

- ✓ Delivery of drugs with narrow absorption window in the small intestine region.
- ✓ Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
- ✓ Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril, etc.
- ✓ Patient compliance by making a once a day therapy.
- ✓ Improved therapeutic efficacy.
- ✓ Improved bioavailability due to reduced.
- ✓ P-glycoprotein activity in the duodenum.
- ✓ Reduces frequency of dosing.
- ✓ Targeted therapy for local ailments in the upper GI tract.

DISADVANTAGES OF GRDDS[7]

- ✓ Not feasible for those drugs that have solubility or stability problems in gastric fluids not suitable for the drugs that are irritant to gastric mucosa.
- ✓ This system requires sufficient high level of fluids in stomach, so that the drug dosage form float therein and work efficiently. These systems also require the presence of food to delay their gastric emptying.
- ✓ Rafting systems has limitation, that they require high level of fluids in stomach for Rafting and working efficiently. So more water intake is prescribed with such dosage form.
- ✓ In supine posture (like sleeping), Rafting dosage form may swept away (if not of larger size) by contractile waves. So patient should not take Rafting dosage form just before going to bed.
- ✓ Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDS.
- ✓ Bio/mucoadhesive systems have problem of high turnover rate of mucus layer, thick mucus layer & soluble mucus related limitations.
- ✓ Swellable dosage form must be capable to swell fast before its exit from stomach and achieve size larger than pylorus aperture. It must be capable to resist the housekeeper waves of Phase III of MMC.

LIMITATION OF GRDDS

These systems are not suitable for those drugs that have solubility or stability problems in the stomach. There is need of high level of fluid in the stomach for success of these systems. Drugs which under goes first pass metabolism are not suitable for the GRDDS. For example: nifedipine. Drugs that cause irritation in stomach mucosa are not suitable candidates for GRDDS.

POTENTIAL CANDIDATES FOR RAFTING DRUG DELIVERY SYSTEM[8]

- ✓ Drugs that are primarily absorbed in the stomach eg Amoxicillin.
- ✓ Drugs that are poorly soluble in alkaline pH eg Furosemide, Diazepam.
- ✓ Drugs that have narrow absorption window eg Levodopa, Methotrexate.
- ✓ Drugs that degrade in the colon eg. Ranitidine, Metformin HCL.
- ✓ Drugs that disturb normal colonic microbes eg Antibiotics against Helicobacter pylori.

- ✓ Drugs rapidly absorbed from the GI tract eg Tetracycline.
- ✓ Drugs acting locally in the stomach.
- ✓ Narrow absorption window in GI tract, e.g., riboflavin and levodopa
- ✓ Basically absorbed from stomach and upper part of GIT, e.g. Chlordiazepoxide and cinnarazine.
- ✓ Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
- ✓ Locally active in the stomach, e.g., antacids and misoprostol.
- ✓ Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.

DRUGS THOSE ARE UNSUITABLE FOR RAFTING DRUG DELIVERY SYSTEMS[8,9,10]

- ✓ Drugs that have very limited acid solubility e.g. phenytoin etc.
- ✓ Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
- ✓ Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

Table 2: Commonly used drug in formulation of gastro retentive dosages forms

Dosage forms	Drugs
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil
Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone
Powders	Several basic drugs
Films	Cinnerzine

Table 3: Gastro retentive products available in the market

Brand Name	Active Ingredient(s)
Cifran OD ®	Ciprofloxacin
Madopar ®	L-DOPA and Benserazide
Valrelease ®	Diazepam
Topalkan ®	Aluminum -magnesium antacid
Almagate FlatCoat ®	Aluminum -magnesium antacid
Liquid Gavison ®	Aluminium hydroxide,
Conviron	Ferrous sulfate
Cytotec®	Misoprostal

PREPARATION OF RAFT FORMING TABLETS[11,12,13]

Drug, polymer and other ingredients were weighed accurately. All ingredients except the binder, volatile ingredients and lubricant were mixed thoroughly. PVP K30 M was dissolved in sufficient quantity of isopropyl alcohol and added to a powder mixture to prepare a dough wet mass. The prepared wet mass was passed through a 22# sieve. The granules were allowed to dry in a hot air oven and then resifted through a 40# sieve. The granules were collected and other ingredients were added and lubricated. Tablets were compressed by a 12-mm diameter flat punch with the help of a rotary tablet compression machine.

PRELIMINARY SCREENING FOR OPTIMIZATION OF PECTIN[14,15]

Sodium alginate is the main core ingredient for raft formation. It is necessary to check the effect of change in the amount of sodium alginate and pectin on raft strength. In experimental work combination of sodium alginate and pectin are useful for drug release and raft formation and its strength. So various combinations of sodium alginate and pectin has been incorporated on trial and error basis for raft formation and drug release up to 1 hr.

Table 4: Formula of Raft forming Tablet

Ingredients	Quantity taken (mg)
Drug	20
Sodium Alginate	325
Pectin	125
Sodium Bicarbonate	50
Calcium Carbonate	150
Mannitol	143
$PVPK_{30}$	30
Aspartame	20
Talc	18
Magnesium Stearate	9

EVALUATION OF RAFT FORMING TABLETS[16]

General evaluation parameters for tablets are:

I. Pre-Compression Evaluation Parameters

Angle of Repose

The angle of repose of powder blend was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using following formula.

Tan Θ = h/r

Θ = tan h/r

Where, **Θ** = angle of repose, h = height, r = radius.

Bulk Density

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength than a less consolidated one and therefore more resistant to powder flow. The ease with which a powder consolidates can be used as an indirect method of quantifying powder. Apparent bulk density (g/ml) was determined by pouring preserved bulk powder into a graduated cylinder via a large funnel and measuring the **volume** and weight. Bulk density can then be calculated by the following formula.

Bulk density = W/Vo

Where, W = wt. of powder, V = initial volume.

Tapped Density

A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. Tapered density was calculated using the following equations.

Tapped density = W/V_f

Where, W = wt. of powder, V = final volume.

Compressibility Index (Carr's Consolidation Index)

The Compressibility index is measure 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 interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index. The compressibility index is calculated using measured values for bulk density (D) and tapped density (D) as follows:

Compressibility index = Dt-D /D X 100

Where D = Bulk density, D = Tapped density

II. Post-Compression Evaluation Parameters

Tablet Dimensions

Thickness and diameter of five tablets randomly selected were measured using vernier calipers. The Pharmacopoeia states that the extent of deviation in a batch of tablet should not exceed the limit of ± 5% of their determined standard values.

Weight variation test

Twenty tablets were selected at random, weighed and average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 10%.

Friability

For each formulation, a pre-weighed tablet sample (six tablets) was placed in a Roche friabilator (Electrolab, Mumbai, India), which is then operated for 100 revolutions. The tablets were dedusted and reweighed. Conventional compressed tablets that lose < 0.5 to 1% of their weight are considered acceptable.

Hardness

Hardness of tablets was determined using a Pfizer hardness tester (Campbell Electronics, Mumbai, India).

Content uniformity

Twenty tablets were weighted and powdered in a mortar. Accurately weighted a quantity of the powder equivalent to about 20 mg of pantoprazole sodium, diluted to 100 ml wit 0.1 N HCl in 100 ml volumetric flask. It was shaken for 15 minutes and filtered. 1 ml of the filtrate was diluted to 0.1 N HCl. The absorbance of the resulting solution was measured at λmax 282 nm and the content pantoprazole sodium of was calculated from the absorbance obtained.

Raft strength measurement by in-house method

A tablet powder equivalent to unit dose was transferred to 150 ml of 0.1 N HCl and maintained at 37°C in a 250 ml glass beaker. Each raft was allowed to form around an L-shaped wire probe (diameter: 1.2 mm) held upright in the beaker throughout the whole period (30 min) of raft development. [Raft strength was estimated using the modified balance method. Water was added drop wise to the pan and the weight of water required to break the raft was recorded.

Note: A double-pan dispensing balance was modified for raft strength measurement. One pan of the dispensing balance was replaced with an L-shaped wire probe as shown in Figure 1.

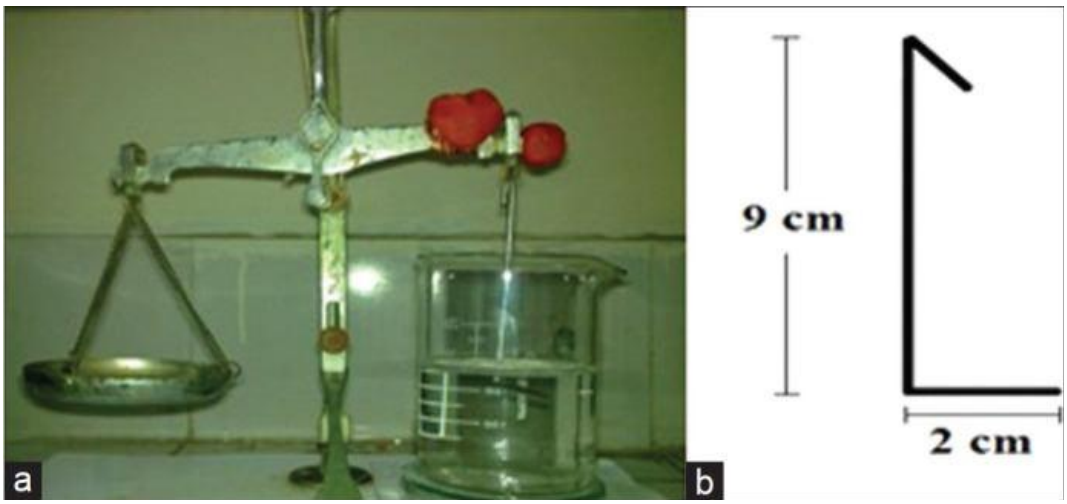

Figure 3: (a) Modified balance method. (b) Wire probe for raft strength measurement

Acid neutralization capacity

A tablet powder equivalent to unit dose was transferred to a 250 ml beaker; 50 ml of water was added to it and was mixed on a magnetic stirrer for 1 min. A 30-ml volume of 1.0 N HCl was added with continued stirring on the magnetic stirrer for 10 min after addition of the acid. Stirring was discontinued briefly and the gum base was removed using a long needle without delay. The needle was promptly rinsed with 20 ml of water, and the washing was

collected in the beaker; stirring was resumed for 5 min. Titration was begun immediately. Excess HCl was titrated against 0.5 N sodium hydroxide to attain a stable pH of 3.5. The number of mEq of acid consumed by the tablet tested was calculated by the following formula: [Where, N HCI = Normality of HCl; V NaOH = Volume of NaOH required; and N NaOH = Normality of NaOH.

***In vitro* drug release study**

In vitro drug release study of Pantoprazole sodium chewable tablets (n = 3) was performed using USP (United States Pharmacopoeia) apparatus II (TDT-08T; Electrolab) fitted with a paddle (50 r.p.m.) at 37 ± 0.5°C using a simulated gastric fluid (pH 1.2; 900 ml) as a dissolution medium. The tablet was powdered and then added to the dissolution medium. At pre-determined time intervals, 10-ml samples were withdrawn, filtered through a 0.45-µm membrane filter and analyzed at 265 nm using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve, which was developed in the range 5-25 µg/ml for 0.1 N HCl.

Raft strength measurement by Texture Analyzer

The raft strength of the most satisfactory formulation (batch F5) was determined by a sophisticated instrument called Texture Analyzer (Brookfield QTS). Powder of tablets equivalent to unit dose was transferred to 150 ml of 0.1 N HCl and maintained at 37°C in a 250 ml glass beaker. The raft was allowed to form around an L-shaped wire probe (diameter: 1 mm) held upright in the beaker throughout the whole period (30 min) of raft development. After 30 min of raft development, the probe was pulled vertically up through the raft at a rate of 30 mm/min. The force required to pull the wire probe up through the raft was recorded by the Texture Analyzer.

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Drug–excipient compatibility study

Fourier transform infrared spectrophotometry

A drug–excipient interaction plays a vital role in the release of drug from the formulation. Fourier transform infrared (FTIR) spectroscopy has been used to study the physical and chemical interactions between drugs and excipients.

Differential scanning calorimetry study

Differential scanning calorimetry (DSC) study was carried out using the Shimadzu DSC-60 (Shimadzu) instrument to check drug–excipient compatibility. The DSC thermograms of the pure drug Pantoprazole sodium and of the physical mixtures of Pantoprazole sodium with excipients were obtained. DSC aluminum cells were used as a sample holder and a blank DSC aluminum cell was used as reference. A 2- to 3-mg weight of sample was used for analysis. Thermograms were recorded over the range 50-300°C.

Stability studies of the optimized formulation

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess drug and formulation stability, short-term stability studies were done for 1 month. The stability studies were carried out on the most satisfactory formulations (batch F5). The most satisfactory formulations were sealed in aluminum packaging and kept in a humid chamber maintained at 40 ± 2°C/75 ± 5% relative humidity (RH) for 1 month. The optimized formulation sealed in aluminum foil was also kept at room temperature and humid condition. At the end of the storage time, the samples were analyzed for raft strength, *in vitro* drug release and % drug content. The *in vitro* drug release profiles for both formulations (initial and after storage at 40 ± 2°C/75 ± 5% RH for 1 month) were compared by the similarity factor (*f*2).

APPLICATION OF RAFTING DRUG DELIVERY SYSTEMS[17]

Rafting drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained drug delivery

FDDS can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. E.g. Sustained release Rafting capsules of Nicardipine Hydrochloride.

Site-specific drug delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. E.g. Riboflavin and Furosemide.

Absorption enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as Rafting drug delivery systems, thereby maximizing their absorption. E.g. A significantly increase in the bioavailability of Rafting dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

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