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FLOATING EXTENDED RELEASE TABLET OF ORNIDAZOLE

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Abstract

The objective of the present study was to formulate a extended release gastro-retentive tablet formulation of ornidazole in order to improve the efficacy of the delivery system in the eradication of *Helicobacter pylori* infection from the stomach. HPMC K4M and 100M were used as matrix-forming polymers and PVP K30 as binder. Sodium bicarbonate was taken as buoyancy contributor. The floating matrix tablets were prepared by wet-granulation method and 23 full factorial design was adapted taking HPMC K4M , HPMC 100M and NaHCO3 as independent variables. All formulations were evaluated for weight variation, content uniformity, hardness, friability, *in-vitro* buoyancy and drug release. The study showed that the tablets remained buoyant in 0.1N HCl over a period of 8 hours and were capable of releasing drug over 8 hour. Analysis of the dissolution data revealed that the kinetic of drug release follows Peppas-Korsemeyer model indicating non-Fickian anomalous diffusion mechanism. ANOVA was done to understand the effect of independent variables on the floating lag time and the cumulative % drug release at 1hr, 2hr, 4hr, 6hr and 8hr using Design-Expert software version 8.1. The study showed that HPMC K4M has more drug- release-retarding capacity than that of HPMC 100M. The formula F_8 showed floating lag time of 2 mins and 45% drug release at 8 hours.

Introduction

A drug delivery system is a therapeutic system which contains one or more drugs and releases the drug (s) to the proper site in the body to produce the maximum simultaneous safety, effectiveness and reliability[1]. The delivery devices are expected to be capable of presenting the drug in its active form at right site, at right time, at right rate and over a right period of time. There are different types of pharmaceutical dosage forms or delivery systems broadly subdivided into two groups:

1. Peroral drug delivery systems (tablets, capsules, solutions, suspensions, emulsions etc.)

2. Non-oral drug delivery systems (TDDS, aerosol, injections, implants, etc.) Peroral drug delivery systems are the commonest mode of drug administration. Some advantages are there:

- It is safer.
- More convenient.
- Does not need assistance.
- Noninvasive, often painless.
- The medicament needs not to be sterile so it is cheaper.

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LIMITATIONS OF ORAL ROUTE

1. Action is not so prompt compared to i.v. or i.m. routes.
2. Unpalatable drugs are difficult to administer. They need coating or encapsulation.
3. May cause nausea and vomiting.
4. Cannot be used for uncooperative, unconscious, vomiting patients.
5. Certain drugs are not absorbed from oral route (streptomycin).
6. Some drugs are destroyed in gastric juice (proteins or peptide drug).
7. Poor bioavailability of the drugs with first pass effect.

commonest, convenient and potential drug delivery system till the date. The peroral delivery systems are broadly subdivided into two categories:

Conventional Peroral Dosage Forms

Novel Peroral Dosage Forms

CONVENTIONAL PERORAL DOSAGE FORMS

Conventional peroral dosage forms such as tablets, capsules, suspensions, solutions, emulsions, etc. release their active ingredients into an absorption pool immediately in the g.i.tract. A conventional oral dosage form produces a bell-shaped drug-blood-level vs time profile that indicates that this type of dosage form cannot maintain drug blood level or drug concentration at site of action within the therapeutic range for extended period of time.

The short duration of action is due to the inability of conventional dosage form to control temporal delivery of the drug. One attempt may be made to maintain drug conc. either in the blood or at the site of action in the therapeutic range for longer period of time by administering a high initial dose to attain a high initial plasma conc. this approach obviously is undesirable and unsuitable. An alternate approach is to administer the drug repetitively using a constant dosing interval, as in multiple dose therapy. In this case, the drug-blood-level reached and the time required to reach that levels depend on the dose and dosing interval. There are several potential problems in multiple dosing 2:

1. If the dosing interval is not appropriate for the biological half-life of the drug, large “peaks” and “valleys” in the drug blood level may result. For examples, drugs with short half-lives require frequent dosing to maintain constant therapeutic level.

2. The drug blood level may not be within the therapeutic range at sufficiently early time, an important consideration for certain disease states.

3. Patient non-compliance with the multiple dosing regimens can result in failure of this approach.

To overcome these problems different novel oral controlled release dosage forms have been designed. In the next chapter these types of dosage forms have been outlined.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Effort to develop efficient gastroretentive drug delivery systems had been started from about 1990 following the discovery of Helicobacter pylori by Warren and Marshall, with the intention of delivering anti-H.pylori drugs locally in the stomach over a prolonged period of time to eradicate the bacteria more efficiently in the treatment of H.pylori mediated gastric ulcer[1]. Later this strategy has been tried to develop rate-controlled oral dosage form to achieve increased bioavailability and predictable and reproducible plasma drug conc. vs. time profile and other pharmacokinetic parameters from the delivery systems[2]. The rate and extent of drug absorption depend on the physicochemical characteristics of the drug molecule, the physiological environment of the absorption site and the residential time of the delivery device at the absorption site. Therefore uniform drug release following absorption of a particular drug can be obtained only when the drug can be made available at the absorption site from a particular environment throughout the whole period of drug release from the delivery system. But this faces difficulty due to highly variable nature of the gastric emptying rate and the existence of different pH region along the g.i. tract. This type of difficulties can be overcome by lodging the delivery device in the stomach for the entire period of drug release. But prior to design and develop gastroretentive delivery device it is necessary to consider the physiological aspects of stomach. In the following sections of this chapter we will focus the physiology of stomach and different approaches towards gastric retention with some special cases for eradication of H.pylori.

PHYSIOLOGIC CONSIDERATION

The intrinsic properties of the drug molecule and the target environment for delivery are the major determining factors in bioavailability of the drug. Factors such as pH,enzymes, nature and volume of secretions, residence time, and effective absorbing surface area of the site of delivery play an important role in drug liberation and absorption. In stomach there are several types of cells that secrete up to 2–3 liters of gastric juice daily. For example, goblet cells secrete mucus, parietal cells secrete hydrochloric acid, and chief cells secrete pepsinogen. The contraction forces of the stomach churn the chyme and mix it thoroughly with the gastric juice. The average length of the stomach is about 0.2 meter, and the apparent absorbing surface area is about 0.1m[2]. A brief survey of relevant physiological features that pose challenge to the development of an effective gastroretentive delivery system is presented below.

Gastric pH

The gastric pH is not constant rather it is influenced by various factors like diet, disease, presence of gases, fatty acids, and other fermentation products . In addition, the gastric pH exhibits intra-as well as inter-subject variation. This variation in pH may significantly influence the performance of orally administered drugs. Radiotelemetry, a noninvasive device, has successfully been used to measure the gastrointestinal pH in human. It has been reported that the mean value of gastric pH in fasted healthy subjects is 1.1±0.15 [5-7].On the contrary, the mean gastric pH in 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 hours. However, in fasted state, basal gastric secretion in women is slightly lower than that of in men. Gastric pH may be influenced by age, pathological conditions and drugs. About 20% of the elderly people exhibit either diminished (hypochlorhydria) or no gastric acid secretion (achlorhydria) leading to basal pH value over 5.0.Pathological conditions such as pernicious anemia and AIDS may significantly reduce gastric acid secretion leading to elevated gastric pH In addition, drugs like H2 receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion. The pH in the proximal duodenum may rise as high as 4 pH units from the stomach. This increase in pH is caused by the bicarbonate secreted by the pancreas and the duodenal mucosa that neutralize 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 the fasted 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 7.5. Gastric pH is an important consideration in selecting a drug substance, excipients, and drug carrier(s) for designing intragastricdelivery systems.

Gastrointestinal Motility and Transit Time

Based on fasted and fed states of the stomach, two distinct patterns of gastrointestinal motility and secretions have been identified. In the fasting state, the stomach usually contains saliva, mucus, and cellular debris. The fasted state is associated with some cyclic contractile events commonly known as migrating myoelectric complex (MMC). Liquid components easily pass through the partially constricted sphincter. On the contrary, the large undigested materials are retained by an "antral-sieveing" process and are retropulsed into the main body of stomach and remain in the fed state. In the fed state, gastric contractions move the contents towards the antrum and the pyloric sphincter. Usually a series of interdigestive events take place in the stomach. However, feeding disrupts this cycle causing a period of irregular contractile pattern. The MMC, which governs the gastrointestinal motility pattern, has been described as an alternating cycles of activity and quiescence. Apparently there are four consecutive phases of activity in the 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. A simplified schematic representation of the motility pattern, frequency of contraction forces during each phase, and average time period for each period is shown in Figure 1.

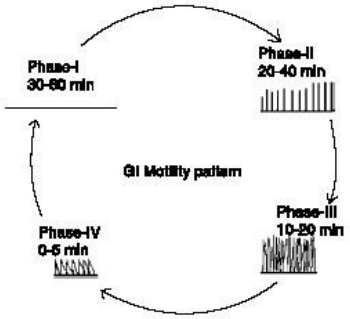


Figure 1: Schematic representation of interdigestive motility pattern.

The different phases originating in the foregut continue to the terminal ileum cycle in about 2 hours. Therefore, when one phase III reaches the terminal ileum, another begins in the stomach and duodenum. As mentioned before, feeding disrupts this cycle resulting in a period of irregular contractile activity, which may last for many hours (i.e., 3 to 4 hours). Thus frequent feeding may prolong gastric retention time.

FACTORS AFFECTING GASTRIC RETENTION

There are several factors that can affect gastric emptying (and hence GRT) of an oral dosage forms. These are discussed below:

1.Density- Density of the dosage form should be less than 1.0 gm/ml for floating and high density systems should have density of about 2.5 gm/ml for efficient gastric retention.

2.Size and Shape – Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm. Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pound per sq.inch. are reported to have better GRT = 90-100% retention at 24 hours compared with other shapes.

3.Single or multiple unit formulation- Multiple unit dosage forms show a more predictable floating profile and permit larger margin of safety against dosage forms failure compared with single unit dosage forms.

4.Fed and unfed state- under fasting conditions, the g.i. motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2.0 hours. The MMC sweeps undigested materials from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

5.Nature of meal- Feeding of indigestible polymer of fatty acid salts can change the motility pattern of the stomach to fed state, thus decreasing the gastric emptying rate and prolonging gastric retention.

6.Caloric content of food- GRT can be increased by 4-10 hours with a meal that is high in proteins and fats.

7.Frequency of feed- The GRT can increase over 400 mins when successive meals are given compared with a single meal due to the low frequency of MMC.

8.Gender- Mean ambulatory GRT in males is less compared with their age and race matched female counterparts, regardless of the weight, height and body surface.

9.Age- Elderly people, especially those over 70 years have a significantly longer GRT.

10. Posture- GRT varies between supine and upright ambulatory states of the patient.

11. Concomitant intake of drugs- The drugs such as anti-cholinergic (Atropine sulphate, Propanthelin), opiates (codeine) increase the GRT by decreasing peristalsis, whereas prokinetic drugs like cisapride, metoclopramide decrease GRT.

12. Biological factors- Diabetes or Chron's disease affect the GRT of the dosage forms.

DEVICES DEVELOPED AS PLATFORM FOR GASTRICRETENTION

A. High Density systems

B. Floating systems

1. Hydrodynamically Balanced system- HBS™

2. Gas generating systems

3. Raft forming systems

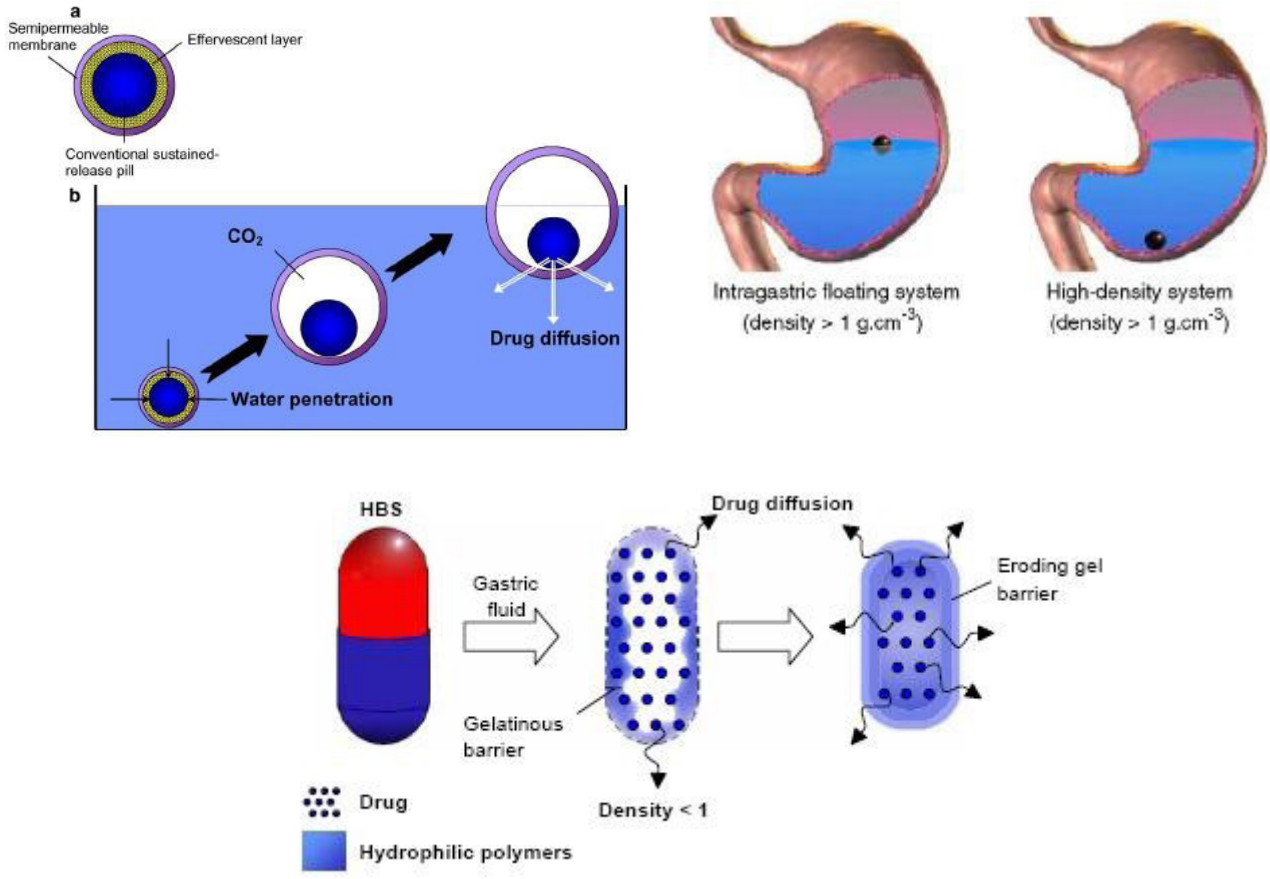


Figure 2: Schematic localization of an intra-gastric floating system and a high density system in stomach.

4. Low density core systems

C. Unfold able , Extendible and Expandable systems

D. Super porous hydrogels

E. Mucoadhesive systems

F. Magnetic systems

AHigh Density Systems

High-density devices utilize weight as a retention mechanism. As the density of the device is larger than that of gastric juice, the device settles down to the bottom of the stomach, as shown in Figure 2. For veterinary applications, the high-density devices are made of heavy materials such as steel cylinders or steel balls. Such devices work well in ruminants, but obviously cannot be applied to humans. There are limits to the density of oral dosage forms for humans, as well as to the size of oral dosage forms based on a high-density mechanism.

B Floating Systems

The main concept here is to use devices in which density is lower than that of water so that the devices can float on top of the gastric fluid. This is expected to prolong the gastric residence time and thus increase the bioavailability of drugs that are mainly absorbed in the upper part of the GI tract. The devices may acquire low density after administration

to the stomach or possess low density from the beginning. There are various types of floating systems that are discussed below:

Hydrodynamically Balanced System (HBS□)

A hydrodynamically balanced system (HBS) was the first formulation that used the floating property of a device with density lower than that of water. HBS is simply a capsule containing a mixture of drug, gel-forming hydrophilic polymers (e.g.,hydroxy-propyl methyl cellulose), and such other excipients as hydrophobic fatty materials (e.g., stearates). Upon contact with gastric fluid after oral ingestion, the capsule shell dissolves and the drug-hydrocolloid mixture absorbs water swells to create a soft gelatinous outside surface barrier. Since the relative integrity of the overall shape is maintained, the density of the system at this stage becomes □1, mainly because of the presence of a dry mass in the center as well as the presence of stearates, which slow down the penetration of water to the inside. As the hydrated outer layer is eroded, a new gelatinous layer is formed. During this process, the drug in the hydrated layer is thought to be released by diffusion.(Figure 3)

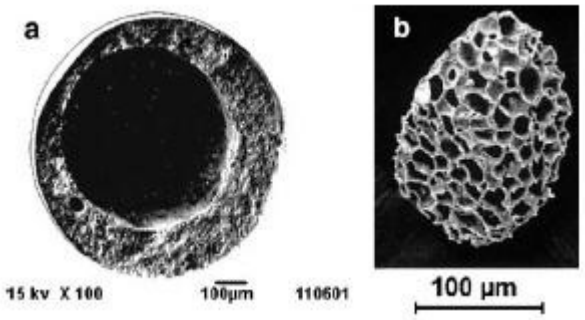


Figure 3: HBS System.

Gas-generating systems :

The gas-generating floating systems lower density by generating gas bubbles in the matrix. Usually CO_2 is generated from sodium bicarbonate at an acidic pH. For this reason, acids such as citric or tartaric acid are included in the formulation. The system may be composed of single- or multi-layers in various geometries such as membranes or spheres. The gas-generating unit can be incorporated in any of the multiple-layers. Alternatively, the gas-generating unit can be loaded inside microparticles such as ion-exchange resin beads coated with a semipermeable membrane. On contact with gastric acid, CO_2 is released, which causes floatation of the device. (Figure 4 & 5)

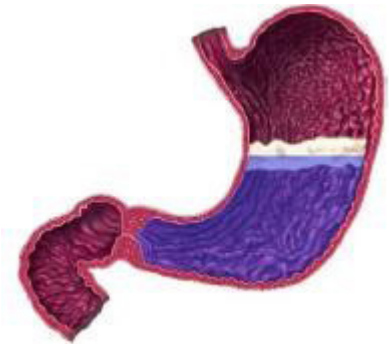


Figure 4: Gas-generating system (a) monolayer system (b) bilayer without semipermeable membrane (c) bilayer with semipermeable membrane.

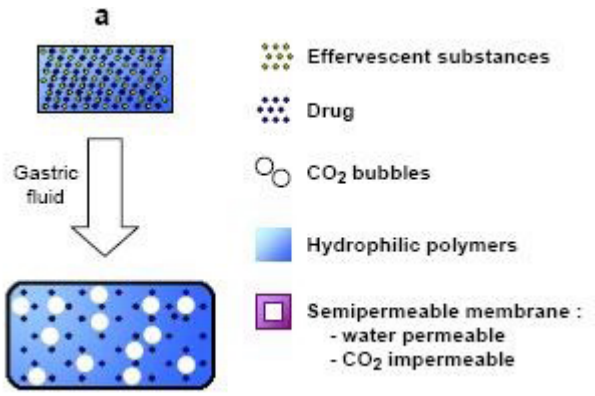


Figure 5: Schematic representation of floating pill.

Raft Forming System

It is a gel-forming solution (e.g., sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles (Figure 6) on contact with gastric fluid. Raft forming systems produce a layer on the top of the gastric fluid. Usually antacids such as aluminium hydroxide or calcium carbonate are incorporated in raft forming systems to reduce gastric acidity.A marketed raft forming system is Liquid Gaviscon□ (GlaxoSmithkline) used in the treatment of gastroesophageal reflux.

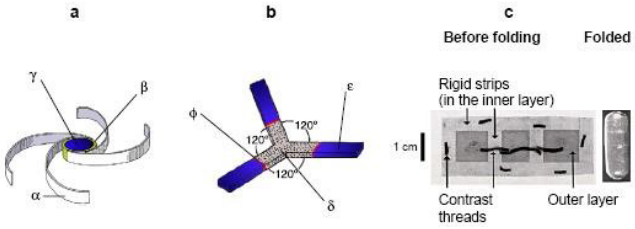


Figure 6: Schematic illustration of the barrier formed by a raft forming system.1`

Low-density Core System

In this type of system, the core materials are made of low-density materials such as empty hard gelatin capsules, polystyrene foams, pop-rice grains, or concave-moulded tablet shells. By proving a buoyant property from the beginning, the device is thought to have a better chance to stay afloat in gastric juice. The external surface of the low density materials are coated with drugs and subsequently with a variety of polymers, such as cellulose acetate phthalate or ethyl cellulose, to control drug release characteristics. Low-density systems can also be produced using hydrogel matrices, such as agar, carrageenan, and alginic acid, which contain light mineral oil. The presence of entrapped oil air provides the buoyancy effect. Hollow microspheres(microballoons) are also included in this type of system. (Figure7)

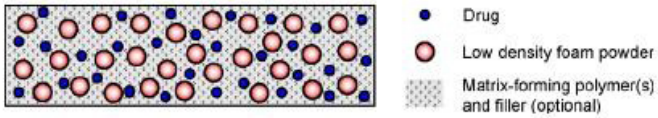


Figure 7: (a)micriballoon (b) foam particles (below) low density,

floating matrix tablet

C Unfoldable, Extendible or Expandable Systems

Systems unfolding in the Stomach

Systems that unfold in the stomach have one or more noncontinuous compressible retention arms. The retention arms are initially folded to make the whole system smaller, with the arms folded, the system can be fit into gelatin capsules or the foldedarms can be fixed by a gelatin band. In the stomach, the compressed or folded retention arms are expanded to make thewhole system too large to resist gastrictransit. This system is made of biodegradable or erodable polymer. (Figure 8)

Figure 8: unfoldable system: (a) α: retention arms, β: receptacle, γ: controlled release tablet (b) δ: shape memory material, ε: erodable material, Φ: component connecting δ and ε (c) gastroretentive dosage form before and after folding

2.4.C.2. Systems Extending to Complex Geometric ShapesStudies have shown that devices that extend in the stomach to certain geometric shapes can prolong gastric retention time. The geometric shapes include lobules, disc, ring, and tetrahedron. Since these devices should be small in the beginning for easy swallowing, they have to be compressible to a small size and expandable to a size large enough to prevent emptying through the pylorus. (**Figure 9**)

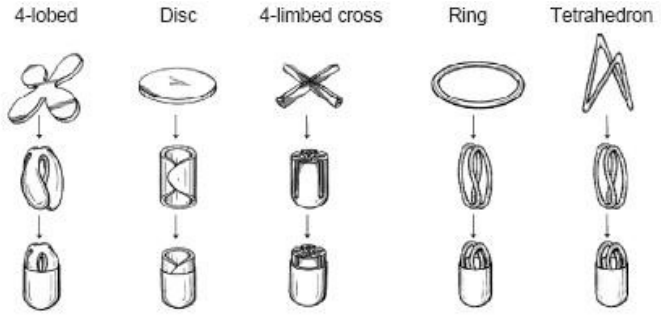


Figure 9: Different geometric forms of unfoldable systems.

System Expanding to Larger Size

These small devices expand in the stomach to a size too large to pass through the pylorus. The devices are made of biodegradable or erodable polymers. Usually these systems contain swellable component such as hydrophilic colloids, osmotic expanding agents (sugars, salts), swellable resins or solidified or liquefied gas at ambient temperature. The liquefied or solidified gas in compartment will vapourize at physiological temperature to produce gas that inflates the device from a collapsed state to an expanded state. Gases that have a boiling point lower than 37□C can be used. Examples of such gases are diethyl ether (b.p. 34.6□C), methyl formate (b.p.31.5□C) etc. (**Figure 10**)

D Superporous Hydrogel system :

Superporous hydrogel swells upon contact with gastric fluid. The extent of swelling of superporous hydrogel is enormously higher than conventional gel. Swelling factor of superporous hydrogel is □1000 whereas, in case of other gel it is 2 to 50. The main difference between hydrogel and superporous hydrogel is pore size. The size of the pores between polymer chains of conventional gel are within molecular dimensions (a few nanometer), but the size of the pores in superporous hydrogel is larger than 100 nm,usually in the range of several hundred micrometer. Superporous hydrogels swell to eqillibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. (**Figure 11**)

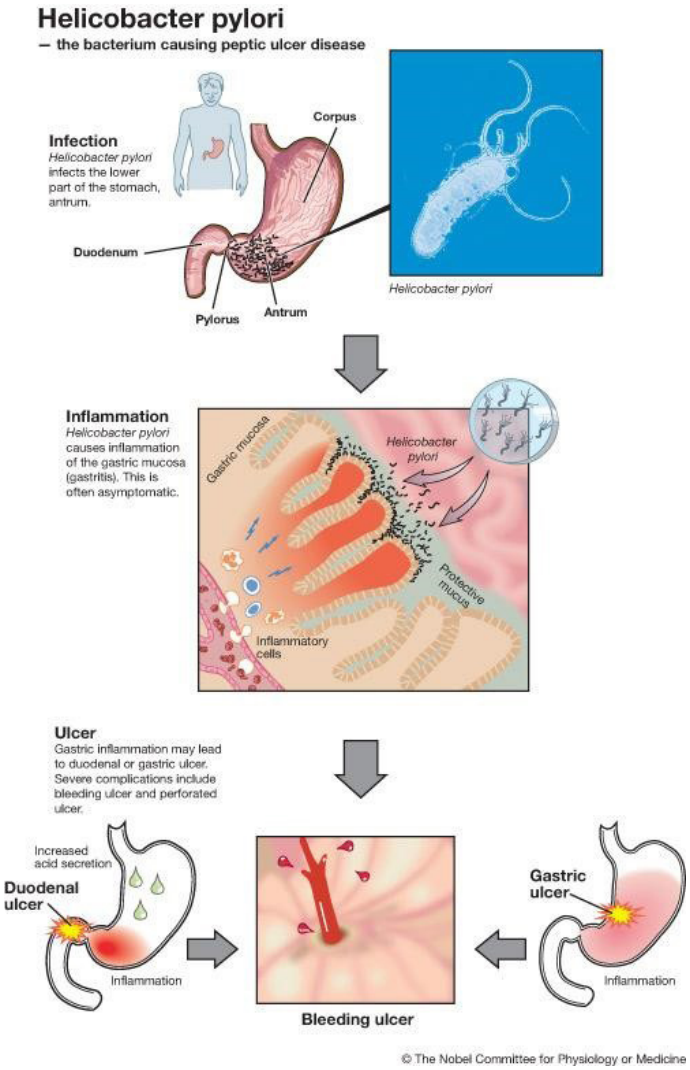


Figure 10: Swellable system

Figure 11: (a)Superporous hydrogel in dry (left),(b) water-swollen state, (on the right) transit of superporous hydrogel

E Mucoadhesive Systems

These systems can stick to the mucosal surface of the gastric tissue and remain in the stomach for a prolonged period of time. Different theories are suggested to explain the mechanisms of bioadhesion. Firstly, the electronic theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material.

Secondly, the adsorption theory suggests that bioadhesion is due to secondary forces such as Vander Waals forces and hydrogen bonding. The wetting theory is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucus layers, and finally, the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate. Materials commonly used for bioadhesion are poly (acrylic acid) (Carbopol, polycarbophil), chitosan, Gantrez (Polymethyl vinyl ether/maleic anhydride copolymers), cholestyramine, tragacanth, sodium alginate, HPMC, sephadex, sucralfate,polyethylene glycol, dextran, poly (alkyl cyanoacrylate) and polylactic acid. Even though some of these polymers are effective at producing bioadhesion, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract. Furthermore, the stomach content is highly hydrated, decreasing the bioadhesiveness of polymers.

F Magnetic Systems

Magnetic systems are usually constructed from a hydrophilic matrix tablet containing a small internal magnet (e.g., magnesium ferrite). An extracorporeal magnet is placed and fixed over the position of the stomach to control GI transit of the dosage form.

Advantages of GRDDS

1.Sustained release: usually, the GI transit time of most drug products is approximately 8-12 hours. For this reason peroral sustained release DDS cannot be designed over 12 hours. But gastric retention approaches can be tried for 24 hour sustained drug release (Once-daily formulation).

2.Predictable drug release and plasma drug conc. vs. time profile: The plasma drug conc. vs. time profile from a dosage form depends on the drug release kinetics of the dosage form. But due to highly variable nature of gastric emptying rate the release kinetic varies greatly and thus leads to a very unpredictable plasma drug conc. Profile. Localization of the delivery systems in the stomach for the entire period of drug release can provide an environment for consistent and uniform drug release and can help to achieve a more predictable plasma drug conc. vs. time profile.

3.Site specific drug delivery: A floating dosage form is a feasible approach especially for the drugs such as furosemide and riboflavin which have narrow absorption window in the upper small intestine and for the drugs which are primarily absorbed from the stomach.

FDDS present these drugs at its mai absorption site and bioavailability increases.

4.Local action in the stomach: sometimes local action of some drugs in the stomach is desirable for the prolonged period of time, especially for the eradication of Helicobacter pylori, which is now believed to be the causative organism for chronic gastritis. Peptic ulcer and stomach cancer. Although the bacterium is highly sensitive to most antibiotics, its eradication from patients requires high conc. Of drug be maintained within the gastric mucosa for a long duration, which is more difficult systemically, but it can be achieved more easily by releasing drugs locally in the stomach for a long period of time. Thus it can be expected that local delivery of anti H. pylori-drugs through GRDDS may result in complete removal of the organism. Antacids can also be incorporated in GRDDS to reduce hyperacidity in the stomach.

5.Enhanced bioavailability: There are some drugs such as chlordiazepoxide, diazepam, cinnarizine, which are poorly soluble at intestinal pH and dissolution is the main rate limiting step in the absorption from the intestine, which leads to wastage of drug and their poor bioavailability. It has been found that FDDS enhances the bioavailability of these drugs.

6.GRDDS can be explored to deliver the drugs (e.g., captopril) orally that are degraded at intestinal pH.

LIMITATION OF GRDDS

1.FDDS requires a sufficiently high level of fluid in the stomach for the system to float therein to work efficiently. This limitation can be overcome by coating the system with bioadhesive polymers, thereby enabling them to adhere to mucous lining of the stomach wall. Alternatively, the dosage forms may be administered with a glass of water (200-250 ml).

2.GRDDS are not feasible for those drugs that have low solubility or stability problems in gastric fluid.

3.Drugs such as Nifedipine which are well absorbed along the entire GI tract and which undergoes significant first-pass metabolism, may not be desirable candidates for GRDDS since the slow gastric emptying may lead to reduced systemic bioavailability.

4.The drugs that are irritant gastric mucosa are not feasible candidates for GRDDS.

EVALUATION OF GRDDS

The parameters that need to be evaluated in gastroretentive formulations include in vitro floating lag time, floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms (tablets). In the case of multiparticulate dosage forms, differential scanning calorimetry (DSC),particle size analysis, flow properties, surface morphology, and mechanical properties are also performed. In case of mucoadhesives, bioadhesion test is to be performed[8].The tests for floating ability and drug release are generally performed in simulated gastric fluid at 37˚C. Gastric retention capacity of the dosage form should be evaluated

in animal and human model by γ-scintigraphy or Roentgenography .

MARKETED GRDD PRODUCTS

- Valrelease®- an HBS (Floating capsule of Diazepam)
- Madopar®- an HBS (combination of levodopa and benserazide)
- Liquid Gaviscon®- a raft forming solution (aluminium hydroxide)
- Alginate Flot-Coat®- a raft forming system (antacid preparation)
- Topalkan®-a raft forming system (antacid preparation)

CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired drug concentration. This idealized objective points to the two aspects most important to drug delivery, namely, spatial placement and temporal delivery of a drug. Spatial placement relates to targeting of a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to target tissue. An appropriately designed sustained release drug delivery system can be a major advance towards solving these two problems. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow for spatial placement as well. Controlled drug delivery can be defined as delivery of the drug at a predetermined rate and/or to a location according to the needs of the body and disease states for a definite time period [1].

Terminology

Over the years, there have been several attempts to classify long acting oral dosage forms. This terminology problem is compounded because various indexing and abstracting services have also not adopted any uniform language when indexing such dosage forms. There are four major groups in these types of preparations [2].

Delayed release systems

These systems are either those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form or an enteric delayed release system. Examples of delayed-release systems include repeat-action-tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating.

Extended release systems

Extended release systems include any dosage form that maintains therapeutic blood or tissue level of the drug for a prolonged period. If the system can provide some actual therapeutic control, whether this is temporal or spatial or both, of drug release in the body, it is considered a controlled delivery system. This explains why extended release is not equivalent to controlled release.

Site specific release systems

Drug action can be localized by spatial placement of a controlled release system (usually rate-controlled) adjacent to or in the diseased tissue or organ [3].

Receptor targeting release systems

These delivery systems utilize carriers or chemical derivatives to delivery drugs to a particular ‘target’ receptor.

Requirements of a controlled drug delivery system

A controlled drug delivery system must fulfill one or several of the followingrequirements.

(a) Extend drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects that may be associated with a saw-tooth kinetic pattern of conventional release.

(b) Localize drug action by placing a controlled delivery system (usually rate-controlled) adjacent to or in a diseased tissue or organ.

(c)Target drug action by using carriers or chemical derivatives to

deliver a drug to a particular target cell type.

(d) Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

Rationale for controlled release delivery systems

The basic logic for controlled release delivery systems is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active chemical moieties by using novel drug delivery systems or by modifying the molecular structure or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate-controlled dosage form and less or not at all a property of the drug molecule’s inherent kinetic properties. Thus, optimal design of a controlled release system necessitates a thorough understanding of the pharmacokinetic and pharmacodynamics of the drug.

Objectives and potential advantages of controlled release systems[4]

- To reduce dosing frequency.
- To provide more constant therapeutic drug level.
- To obtain more uniform pharmacological response, or in other words, less potentiation or reduction in drug activity with chronic use.
- To reduce total amount of drug used.
- To reduce inconvenience to the patient and increase compliance.
- To avoid night time dosing.
- To reduce gastrointestinal irritation.
- To reduce both local and systemic side effects.
- To reduce fluctuations in circulating drug levels and minimization of drug accumulation in body tissues with chronic dosing.
- To allow the use of drug with low therapeutic index.

Possible disadvantages of controlled release systems

Possibilities of dose dumping.

Reduced potential for accurate dose adjustment.

Increased potential for first pass metabolism.

Possible reduction in systemic availability.

Drug release profile restricted to residence time in gastrointestinal tract.

Difficulty or impossibility of quick stoppage of pharmacological action of drugs, when serious poisoning or intolerance occurs.

Little or no efficacy of dosage forms if the drug is not absorbed by intestinal mucosa [5]. Greater cost than conventional dosage forms [5].

DRUG PROPERTIES INFLUENCING THE DESIGN OF CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

To establish a basis for discussion of drug property influencing the controlled release product design, it is worthwhile focusing attention on the two principal elements of the system –

(a) Behavior of the drug in the drug delivery system.

(b) Behavior of the drug in the body.

The first of these two elements concerns itself with the way in which the drug properties can influence the release characteristics from the drug delivery systems. Under normal circumstance with a non-controlled release product, the rate limiting step in drug availability is usually absorption of drug across a biological membrane such as gastro intestinal wall. In a controlled release product on the other hand, one generally aims for release of drug from the dosage form as the rate limiting step so that the availability of drug is controlled by the kinetics of drug release rather than absorption.

The second element, behavior of the drug in body, is an extremely complex picture,

involving the rate of the drug during its transit to the target area as well as its fate while in the biophase. The drug potentially interacts with a variety of substances leading to undesired drug loss as well as desired drug absorption. This undesired drug loss as well as desired drug absorption is a function of the structure and hence the property of the drug as well as the type of the delivery system in which it is housed.

Physicochemical properties of a drug influencing the drug product design and performance

release form, restrict the route of the drug administration and significantly modify drug performance for one reason or another. The properties are as follows:

Dose size [6]:

Erikson has stated that drugs with a single oral dose larger than 0.5 gm are poor candidates for oral controlled release products since the absorption mechanism will, in most cases; generate a substantial volume of the product, depending on the density of the drug, duration of intended prolongation and type of sustaining mechanism. However a compromise between the dose size and the efficacy should always be sought.

Aqueous solubility:

Extremes in aqueous solubility are undesirable in the preparation of a controlled release product. The principal reason for this restriction centers on the dissolution rate of the drug. Aqueous solubility of a drug exercises its control on the absorption process in two ways. By its influence on the dissolution rate of a compound which establishes the drug concentration in solution and hence the driving force for the tissue permeation, and By its effect on the ability of the drug to penetrate tissue, which is determined in part by its proportional to its solubility, the aqueous solubility of the drug could be used as a first approximation to its dissolution rate. It has been reported that the drug with water solubility less than 0.1 mg/ml are appropriate to have reduced physiological availability in conventional oral dosage forms [7]. Drugs with greater water solubility are equally difficult to incorporate a sustained release system [8].

Partition coefficient [9]:

It has been shown that a parabolic relationship exists between partition coefficient and membrane permeation extremes. In partitioning behavior, one expects low rates of drug flux and at some intermediate partition coefficient, there should be a maximum rate of permeation in general, drugs with extremely high partition coefficient will readily penetrate into body membranes producing an accumulation in body tissues with subsequent slow elimination.

Drug stability:

The extent of drug loss through hydrolysis or metabolism in the stomach and intestine is proportional to the residence time in these organs and the apparent rate of degradation. Since most oral sustained release systems are designed to release their contents over much of the length of the gastrointestinal tract, drugs which are unstable in the environment of the intestine would be unsuitable to be formulated into such delivery system [10]. Interestingly placement of a labile drug in a sustained release form often improves the bioavailability.

Protein binding:

Mane drugs bind to plasma proteins with a concomitant influence on the duration of drug action. This drug-protein complex serves as a depot for the drug producing a prolonged release. Charged compounds would be expected to have a greater potential for binding than uncharged compounds. The presence of the drug molecules of a hydrophobic chain that is capable of stabilizing the drug-protein complex will make binding especially favorable.

pKa:

The pH partition hypothesis states that the uncharged form of a drug species will be preferentially absorbed through many body tissues. The release of ionizable drug from a sustained release product should be programmed in accordance with variation in pH of the different segments of the GI tract so that the amount of preferentially absorbed uncharged species and the plasma level of the drug would be approximately constant throughout the time course of the drug.

Particle size:

The density of the core is very important in controlling the transit time in the GI tract. Increasing density is the most important factor promoting the retention of pellets in the microvilli. It has been reported that the coated heavy pellets containing barium sulphate of density 1.6 significantly increased the average transit time in ileostomy subjects compared to coated light pellets containing hard paraffin of density 1.0 11, 12 The average transit times were 7 and 2 hours for light and heavy pellets respectively. Subsequently it has been shown that the GI transit time for unmediated, non-disintegrating, hard paraffin tablets was far less reproducible than that of the small pellets [13].

Molecular size:

The ability of a drug to diffuse through membranes, its so-called diffusivity can be influenced by its molecular size as shown by the following equation.

$$\text{Log } D = - S_V \text{ Log } V + K_V = - S_M \text{ Log } M + K_M$$

Where D is diffusivity, M is molecular weight, V is molecular volume and S_V, S_M, K_V, and K_M are constants. Molecular size of a drug is an important that must be considered if a polymeric membrane is relied upo in the controlled release mechanism.

Biological factors

The design of controlled release product should be based on a comprehensive picture of the drug disposition. Each pharmacokinetic property and biological response parameter has a useful range for the design of controlled release products

and outside the range, sustained release product design becomes difficult or impossible.

Absorption:

Drugs that are slowly absorbed or absorbed with a variable absorption rate are candidates for a sustained release system. For oral dosage forms, the lower limit on the absorption rate constant is in the range of 0.25 $hour^{-1}$, assuming a GI transit time of 10 – 12 hours.

Distribution:

For design of controlled release products, one of the important pharmacokinetic parameters to be considered is the apparent volume of distribution. The apparent volume of distribution influences the concentration and amount of drug either circulating in the blood or in the target tissues. It can influence the elimination kinetics of the drug. Thus the drugs with high apparent volume of distribution are poor candidates for controlled release.

Metabolism:

Controlled release systems for the drugs that are extensively metabolized is possible as long as the rate of metabolism is neither too great nor the metabolism is variable with GI transit or other routes. Thus a controlled release product can be as long as the metabolism remains predictable and can be incorporated in the design of these products.

Biological half life:

The rate of elimination of a drug is quantitatively described by its biological half life,$t_{1/2}$. The half life of a drug is related to its apparent volume of distribution V and its systemic clearance. $t_{1/2} = 0.693\ V/Cl_s = 0.693V.\ AUC/\ dose$ The systemic clearance, Cl_s is equal to the ratio of an intravenously administered dose to the total area under the drug blood level versus time curve AUC. A drug with a short half-life requires frequently dosing and this makes it is desirable candidate for a sustained release formulation. On the other hand, a drug with a long half-life is dosed at greater time intervals and thus there is less need for a sustained release system. It is difficult to define precise upper and lower limits for the value of the half-life of a drug that best suits it for sustained release formulation. In general however, a drug with a half-life of less than 2 hours should probably not be used. Since such systems will require unacceptably large release rates and large doses. At the other extreme, a drug with a half-life of greater than 8 hours should also probably not be used. In most instances, formulation of such a drug into a sustained release system is generally unnecessary [14].

Side effects:

For some drugs, the incidence of side effects in addition to toxicity is believed to be related to their plasma concentration. A sustained release system can, at times, minimize side effects for a particular drug by controlling its plasma concentration and utilizing less total drug ever the time course of therapy. The technique of controlled release has been more widely used to lower the incidence of side effects and appears to be beneficial.

Margin of safety of the drug:

For every patent drug whose therapeutic concentration range is narrow, the value of Therapeutic Index (TI) is small. In general, the large value of TI, the safer the drug. Drugs with very small values of TI are usually poor candidates for formulation into sustained release products primarily because of technological limitations of precise control over release rates.

TECHNIQUES OF OBTAINING CONTROLLED RELEASE SYSTEMS

There are three broad categories of obtaining controlled or sustained release systems.

The Biological Methods

These methods have limited applications and are only used by physicians. These approaches consist of administering two drugs in order to modify the biological fate of one of them. For example, oral penicillin is rapidly excreted by the kidney. This effect of penicillin is extended by the administration of probenacid, which interferes with the renal excretion of penicillin. Therefore, penicillin remains in the body providing prolonged action.

The Chemical Methods

The chemical methods of preparing sustained or controlled release drug delivery systems are based on the promise that a drug is first released at some target site within the body and then continues to be

released slowly.

Two approaches have been used to achieve this goal:

The analogue approach:

This method is rarely identified as an approach to sustained or controlled release of drug delivery systems. Synthesis of analogues may alter the solubility, partitioning characteristics, distribution, metabolism, excretion, etc.

The prodrug approach:

This method involves the chemical modification of a compound in order to form a complex that regenerates the active molecule when exposed to body fluids. As an example, one can mention most of the actual sustained release steroids, generating the active molecule through the in vivo hydrolysis of the ester or the ether. The rate of hydrolysis determines the duration of action.

The Pharmaceutical Methods

These methods are based on proving a slow release of the active compound through the dosage form itself. These methods may involve the dissolution and /or diffusion of the drug through the delivery system matrix, the ion exchange, resins etc.

Classification of controlled release systems15, 16:

This classification is based on mechanism that controls release of incorporated drug.

Monolithic Devices (Matrix Systems):

In a monolithic device, the therapeutic agent is intimately mixed in a rate controlling polymer and release occurs by diffusion of the agent from the device. There are two types of devices. In one, the active agent is dissolved in the polymer, whereas in the other, the active agent is dispersed in the polymer. Although the release of the active agent from the monolithic systems does not proceed by zero-order kinetics, it is the simplest and most convenient way to achieve prolonged release of an active agent. Such devices can be conveniently prepared by using simple polymer fabrication techniques involving a physical blending of the drug with a polymer matrix, followed by compression molding, injection molding, extrusion, calendaring, or solvent casting.

The Reservoir Devices (Membrane Devices):

In a reservoir device, the drug is contained in a core that is surrounded by a rate- controlling membrane. Transport of the material in the core through the surrounding nonporous, homogenous polymer film occurs by dissolution at one interface of the membrane and then diffusion down a gradient in the thermodynamic activity. If the thermodynamic activity of the drug in the reservoir remains constant, if there is no change in the rate-limiting membrane characteristics and if infinite sink conditions are maintained at the downstream side of the membrane, rate of drug release will be constant and can be predictable from knowledge of membrane permeability and device configuration. Examples of these devices are – Membranes [17]

Capsules [18],Microcapsules [19,20] Liposomes[21], Hollow fibres [22]

Solvent Controlled Devices:

These devices release drugs as a consequence of controlled penetration of a solvent into device. Although nonaqueous solvent can be used, clearly only water is of importance in controlled release application for human applications. Based on two general mechanisms, osmosis and swelling, there are two types of devices.

Osmotically controlled devices:

In this device, an osmotic agent is contained within a rigid housing and is separated from an active agent compartment by a movable partition. One wall of the rigid housing is a semipermeable membrane so that when the pump is exposed to an aqueous environment, water will be driven osmotically across the membrane; the increased volume within the osmotic compartment will force the active agent out of the device through the delivery orifice.

Swelling controlled devices:

The drug is homogeneously dispersed in a glassy polymer. Because glassy polymers are essentially impermeable, the drug is immobilized in the matrix and no diffusion through the solid polymer phase takes place when such a monolithic device is placed in an aqueous environment, water begins to penetrate the matrix and swelling takes place. As a consequence of the swelling process, chain relaxation takes place, and the incorporated drug begins to diffuse from the swollen layers.

Chemically Controlled Devices:

In a chemically controlled device, rate of drug release from the polymer is controlled by a chemical reaction that can be hydrolytic or enzymatic cleavage of a labile bond, ionization or protonation.

Oral controlled release drug delivery systems:

The oral route has been the preferred route for drug administration in general because it offers more flexibility in dosage form design is relatively safe. The major techniques used in formulating oral drug delivery systems are as follows:

Enteric Coating:

The coating is intended to protect either the stomach from unwanted effects of the drug or the drug from degradation in gastric environment.

Beads or Spheres:

The spansules contain beads or spheres of the drug that are coated with a material that differs in thickness form beads, determining the time at which the drug will be released.

Enteric Coated Beads in Capsules:

This system combines the two previous mentioned strategies. The rate of drug release depends partially on the emptying rate of the beads from the stomach.

Mixed Release Granules:

This method uses granules as by the preparation of compressed tablets. Two or more sets of granules are used. One set, which carries the immediate release component of the drug, is prepared in the

usual manner. The second set contains drug that either coated with slowly digestible or poorly soluble materials or mixed with solution retarding additives.

Erosion Core with Initial dose:

In this method, the sustaining component is formulated as a non-disintegrating tablet that essentially maintains its geometric shape through the GI tract. The initial dose may be contained in a press or pan coated outer shell. Most of these systems are designed as a cylinder more than as a sphere. Erosion on a sphere does decrease total surface in significant way ($4\pi r^2$), while erosion on a cylinder with a large diameter to height ratio does not affect too much release rate.

Matrix Tablets:

A matrix tablet is a tablet in which the drug is embedded in a nondissolving material. Upon ingestion, the drug leaches out by diffusion, leaving behind the inner, porous matrix, which is excreted.

Ion Exchange:

The mechanism of ion exchange can be considered as a chemical reaction of the type _

$$RSO_3\text{-}_{DH}+ \rightarrow RSO_3\text{-}Na + DH$$

Sulfonic acid type cationic exchange resin

This type of resin slowly releases the drug by exchanging with ions as H^+ etc. The rate of the release is dependent on the concentration of ions present in the GI tract.

Complexation:

The preparation of complexes or salts of active drugs that are slightly soluble in the GI fluids gives sustained action. For example, therapeutically active amine drugs form insoluble complexes with tannic acid.

Microencapsulation:

In the microencapsulation technology, particles of drug powder or solutions are coated with a thin coating of polymer behaving as semipermeable membrane. There are several methods for preparation of microcapsules.

The Osmotic Pump:

This is the most recent method for sustained release. It consists of a core tablet and a semipermeable coating with a laser drilled hole, through which drug releases. The system operates on the principle of osmotic pressure. The GI fluids permeate the semipermeable membrane, dissolve the drug in the core and the osmotic pressure forces or pump the drug solution out of the delivery orifice.

NEWER APPROACHES IN OBTAINING CONTROLLEDRELEASE DRUG DELIVERY SYSTEMS

Various potential developments and new approaches have recently been introduced to overcome the problems associated with oral drug administration.

1. Development of a viable drug delivery system, which is capable of administering a drug at a preprogrammed rate for the duration, required for an optimal efficacy.
2. For prolongation of the gastrointestinal residence time, the delivery system

   developed can reside at the vicinity of absorption site for sufficiently long time to deliver the entire dose.
3. For drugs subjecting to an extensive hepatic “first pass elimination”, preventive measures have been developed to minimize the extent of hepatic “first pass” metabolism.

Novel Peroral Drug Delivery Systems

There are a number of novel drug delivery systems, which could be utilized for the controlled delivery of drug in the alimentary canal. They can be outlined as follows:

a. Osmotic pressure controlled drug delivery systems.

b. Hydrodynamic pressure controlled drug delivery systems.

c. Membrane diffusion controlled drug delivery systems

   (i) Microporous Membrane-coated tablets

   (ii) Solubility Membrane-controlled solid dosage forms

   (iii) Enteric Controlled Release Tablets

d. Multi-laminated sustained release tablets

e. pH-independent controlled release granules

f. Polymer coated drug-resin preparations

g. Thixotropic bilayer tablets

3.4.2 Prolongation of Gastrointestinal Transit Time

All of the controlled release drug delivery systems discussed so far will have only limited utilization in the oral controlled administration of drugs if the system cannot remain in the vicinity of the absorption site for life-time of the drug delivery system. The alimentary canal transit time for an indigestible object can vary from 8 to 62 hours. However, 40% of human beings were found to excrete the object within 24 hours. Therefore, the majority of controlled release drug products designed for oral administration have a limited residence time in the vicinity of absorption sites 2 – 3 hours as pointed out by Hofmann et al [23]. So most of the long acting drug products require a dosing schedule of twice a day. Several approaches have recently been developed to extend the gastrointestinal transit time by sustaining the residence time of the delivery systems in the stomach:

- **(i)** Intragastric Floating drug delivery systems
- **(ii)** Gastro-Inflatable drug delivery system
- **(iii)** Intragastric osmotic-controlled drug delivery system
- **(iv)** Intra-rumen controlled release drug delivery system
- **(v)** Bioadhesive oral drug delivery system

Overcoming Hepatic First Pass Elimination

There are a few approaches, which have been undertaken to

overcome this problem.

- Physical approaches
- Chemical approaches
- Buccal and sublingual drug administration
- Transmucosal sustained release troches
- Oral sustained release microcapsules
- Rectal drug administration

HELICOBACTER PYLORI INFECTION

Helicobacter pylori is a gram-negative bacillus responsible for one of the most common infections found in humans worldwide [1]. Warren and Marshall first cultured and identified the organism as Campylobacter pylori in 1982. By 1989, it was renamed and recognized to be associated closely with antral gastritis (gastric and duodenal ulcers in adults and children). In recognition of this crucial discovery, they were awarded the Nobel Prize for medicine in 2005.

By the early-to-mid 1990s, further evidence supported a link between chronic gastritis of H pylori infection in adults and malignancy, specifically gastric lymphoma and adenocarcinoma.

PATHOPHYSIOLOGY

H pylori organisms are spiral-shaped gram-negative bacteria that are highly motile because of multiple unipolar flagella. They are microaerophilic and potent producers of the enzyme urease. H pylori inhabits the mucus adjacent to the gastric mucosa. Important adaptive features that enhance survival of the organism in an acidic environment include its shape and motility, its reduced oxygen requirement, its adhesion molecules that are trophic to certain gastric cells, and its urease production. Bacterial urease converts urea to ammonium and bicarbonate, neutralizing gastric acid and providing protection in the hostile, highly acidic gastric environment. Some of the lipopolysaccharide of the organism mimics the Lewis blood group antigens in structure. This molecular mimicry also helps in the continued existence of H pylori in the unfavorable gastric environment [2]. H pylori produces suspected disease-inducing factors, including urease, vacuolating cytotoxin, catalase, and lipopolysaccharide (LPS). Urease, a potent antigen, induces increased

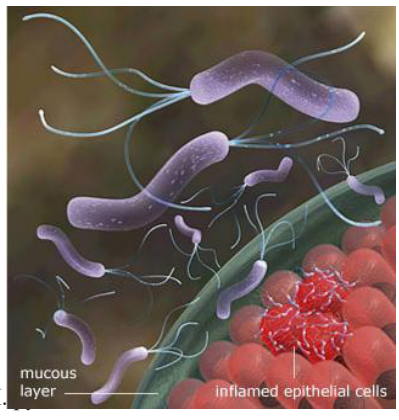


Figure 4.1: H.

cytotoxin, which induces inflammatory cytokines, may be associated with more pronounced inflammation and increased propensity to cause disease. Catalase helps H pylori survive in the host by preventing the formation of reactive oxygen metabolites from hydrogen peroxide. The LPS outer membrane of H pylori is a less potent inducer of the host complement cascade. Cytotoxin-associated antigen (CagA) is probably the most important virulence factor in H pylori. Translocating the CagA protein into the gastric epithelial cells causes rearrangement of the host cytoskeleton and alters cell signaling and perturbs cell cycle control. Furthermore, CagA-positive strains are known to induce the expression of a DNA-editing enzyme, which leads to accumulation of mutations in the tumor suppressor p53 [3]. Two Japanese groups demonstrated the important role of Peyer patches (PPs) in the development of H pylori– induced gastritis. Kiriya et al showed that Helicobacter– induced gastritis was impaired in PP-null mice [4]. Another study by Nagai et al also supports the notion that PPs are inductive sites for generating CD4 T-cell responses in the gastric mucosa [5].H. pylori colonize the stomach, induces inflammatory cytokines, and causes gastric inflammation. Individuals with H pylori– associated antral-predominant gastritis with increased gastric acid production are prone to peptic ulcer disease (PUD) [6]. In contrast, H pylori pan-predominant gastritis or corpus-predominant gastritis with decreased gastric acid production are more prone to developing gastric atrophy (intestinal metaplasia and gastric adenocarcinoma).

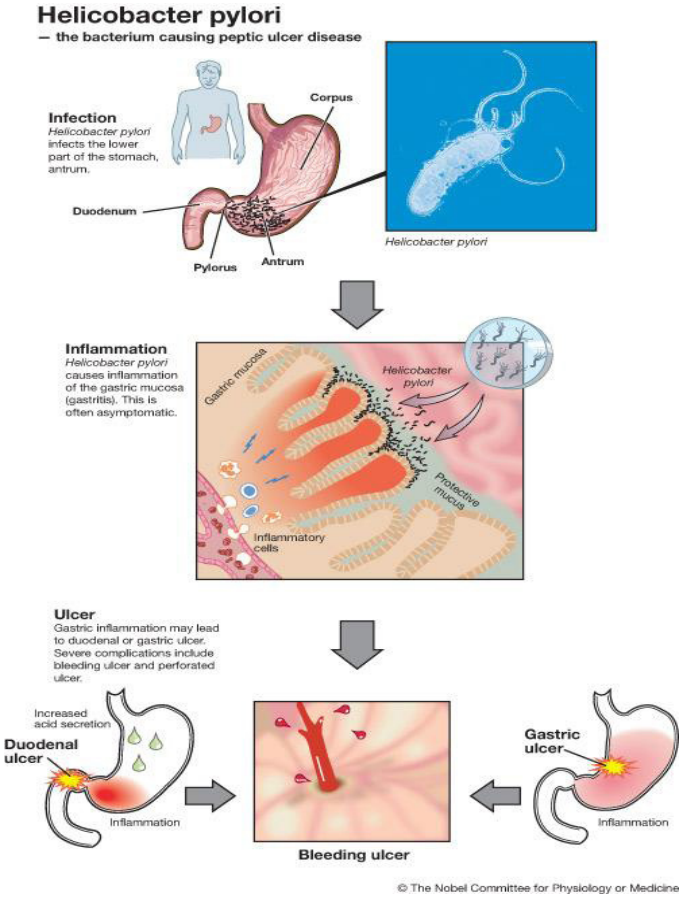


Figure 4.2 Diagramatic representation of H. pylori induced gastric ulcer

immunoglobulin G and immunoglobulin A production. Expression of vacuolating.

H pylori has been associated with iron-deficiency anemia. The 2 main hypotheses that potentially explain this relation are (1) sequestration of iron due to antral H pylori infection and (2) decreased non-heme iron absorption caused by hypochlorhydria. H pylori infection and its association with gastric malignancy have been well described in several epidemiologic studies [7]. However, the course of progression from inflammation to cancer remains unclear. One model describes the stepwise progression of H pylori infection to hypochlorhydria, chronic gastritis, atrophic gastritis, intestinal metaplasia, and gastric cancer. Increased production of the cytokine interleukin 1β has been linked to an increased risk of hypochlorhydria and gastric cancer in infected subjects.

FREQUENCY

In general, the prevalence is high in developing countries and the infection is acquired at a young age. The prevalence of H pylori infection is not only lower in industrialized countries than in developing countries, but the incidence of H pylori infection, gastric cancer, and ulcer disease are also declining. Worldwide, more than 1 billion people are estimated to be infected with H pylori..

MORTALITY / MORBIDITY

Most children infected with H pylori are asymptomatic. Antral gastritis is the most common manifestation in children. Duodenal and gastric ulcers may be associated with H pylori gastritis in adults but is uncommon in children. The risk of gastric cancers, including non-Hodgkin lymphoma (eg, mucosa-associated lymphoid tissue [MALT]) and adenocarcinoma, is increased in adults. The relationship between H pylori gastritis and recurrent abdominal pain (RAP) is controversial. The incidence of H pylori gastritis in patients with RAP is not significantly higher than the incidence of H pylori infection in the general population. Although some studies demonstrate an improvement in symptoms in children with RAP and H pylori gastritis after eradication therapy for H pylori, data from a recent double-blind controlled trial did not confirm that finding[8]. The heterogenicity of theirdefinition of RAP and the varying study methodologies may have led to different results and conclusions. The medical positional statement of the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition regarding H pyloriinfection in children also found no convincing data to support the routine testing of children with RAP for H pylori.

Some studies suggest that H pylori protect human subjects from developing gastroesophageal reflux disease, whereas others postulate a causative association between them. A recent retrospective study revealed a significantly higher prevalence of reflux esophagitis in children with H pylori infection [10]. H pylori infection has also been associated with extraintestinal manifestations, such as short stature, immune thrombocytopenic purpura, and migraine with varying level of evidence.

RACE

The prevalence is increased in black, Hispanic, Asian, and Native American populations.

SEX

Infection rates are similar in males and females.

AGE

In developed countries, less than 10% of children younger than 12 years are infected; however, seropositivity increases with age at a rate of 0.3-1% per year. Studies of seropositivity in adults in developed countries revealed prevalences of 30-50%. In the United States, the estimated prevalence is 20% for people younger than 30 years and 50% for those older than 60 years. In developing countries, the prevalence rates are much higher. The serological prevalence rates of H pylori were 15% and 46% in Gambian children younger than 20 months and age 40-60 months, respectively [11].

CLINICAL

History

When obtaining the history of patients with Helicobacter pylori infection, one should pay particular attention to anorexia and weight loss, pallor or laboratory findings of anemia, vomiting, abdominal pain associated with meals or nighttime, and any description of GI bleeding. A history of such findings raises the concern of peptic ulcer disease (PUD).

In the child in whom H pylori infection is suspected, the history should include the following:

- Character, location, frequency, duration, severity, and exacerbating and alleviating factors of abdominal pain
- Bowel habits and description of stool
- Appetite, diet, and weight changes
- Halitosis, vomiting, and description of gastric material
- Family history of ulcer disease or GI conditions (eg, Crohn disease)
- Medications (prescribed and over the counter)
- Previous diagnostic testing and specific therapy in the GI tract

Physical

Physical examination of an asymptomatic child with H pylori infection usually yields unremarkable findings. In the child with chronic gastritis, duodenitis, and PUD, important examination findings include epigastric tenderness or findings consistent with GI bleeding (eg, guaiac-positive stools, tachycardia, and pallor).

Children with PUD leading to complications (eg, severe blood loss in the GI tract, perforation, obstruction) can appear ill and have evidence of hemodynamic instability or signs of an acute abdomen. Children with long-standing PUD from H pylori may become profoundly anemic from undetected chronic bleeding and have no complaints.

- Assess the general appearance of the child.
- Assess perfusion, with attention to mental status, heart rate, pulses, and capillary refill.
- Assess the skin and conjunctivae for pallor.

· Perform a thorough heart and lung examination.

· Inspect, auscultate, and palpate the abdomen.

· Perform rectal examination and a stool guaiac test.

Causes

Epidemiologic studies have addressed various factors, such as bacterial, host, genetic, and environmental factors, to determine the causative links to H pylori infection. Data support person-to-person spread of infection, possibly related to dental plaque, but knowledge of reservoirs and transmission modes is incomplete.

Causes of H pylori infection include the following:

· Person-to-person transmission of H pylori infection is noted.

· Infection clusters are noted, particularly in families with infected children. The possible routes are fecal-oral, oral-oral and gastro-oral. Mother-to-child transmission was strongly suggested in a study of DNA analysis of the H pylori strains [12]. The data showed identical H pylori strains between mothers and their toddler-aged children. Moreover, the mother's symptoms of nausea and vomiting and the use of pacifier were significantly associated with the risk of H pylori infection in children.

· Crowding and poor personal hygiene may also play a role.

· An increased prevalence of H pylori infection is noted in developing countries. This may reflect the combined effects of poor living conditions, poor hygiene, and crowding.

· In the United States, socioeconomic level is strongly and inversely related to the prevalence of H pylori infection, a finding that may also reflect the same factors as those noted in developing countries.

· Bacterial factors may play a role in the clinical manifestations of H pylori infection.

· Patients with H pylori infection have 2 basic phenotypes based on the presence or absence of a vacuolating cytotoxin.

· People with cytotoxin-positive infection have endoscopically proven inflammation that is more pronounced than those of patients with cytotoxin-negative H pylori infection.

- Host factors may play a role in the acquisition of H pylori infection.

 Children may be better able to clear acute infection than adults (2% per year).

 Hypochlorhydria may be necessary to allow H pylori to colonize in the stomach.

 Normal gastric epithelial cells that line the stomach are necessary for H pylori persistence. H pylori is not found in atrophied metaplastic epithelium.

- Genetic factors may play a role in H pylori infection.
- Concordance for PUD is higher in monozygotic than in dizygotic twins.
- Data from only one study links an increased prevalence of H pylori infection with a community's water supply [13]
- Other possible ways of transmission include vector-borne transmission [14].
- H pylori isolates are found more often in personnel who work in the endoscopy suite than in the general population .

TREATMENT

Medical Care

- Indications for treatment of Helicobacter pylori infection include the following:
- Documented gastric or duodenal ulcer Histologically proven gastric metaplasia
- Gastric mucosa-associated lymphoid tissue (MALT)oma Prior documented gastric or duodenal ulcer with current active infection
- Iron-deficiency anemia refractory to treatment
- Although no compelling evidence suggests treating gastritis without ulcer or nonulcer dyspepsia, many clinicians treat with the intension of aiding symptomatic relief, preventing long-term complications, or both.
- Triple therapy is considered to be the standard treatment for children. A proton pump inhibitor combined with two antibiotics has been shown to be very effective in clearing H pylori from the stomach. The current recommendation is treatment with amoxicillin, clarithromycin, and a proton pump inhibitor for 2 weeks. Triple therapy regimens that are effective in children include a proton pump inhibitor combined with clarithromycin and metronidazole or amoxicillin and metronidazole.
- In adults, triple therapy based on amoxicillin, clarithromycin, and a proton pump inhibitor was shown to be more effective when given for 14 days rather than for 7 days [15].
- Efficacy of the 10-day treatment with proton pump inhibitor–based therapy has not been very widely studied in children and was not recommended in a recent meta-analysis [16].
- Quadruple therapy is used as a second-line treatment. Metronidazole, clarithromycin, amoxicillin and omeprazole were effective, with an eradication rate of 94% [17].
- One trial in children used bismuth-based quadruple therapy and showed an eradication rate of 84% [18].
- One trial has tested the efficacy of sequential therapy in children (omeprazole plus amoxicillin for 5 d, followed by omeprazole, clarithromycin, and tinidazole for

another 5 d); eradication of H pylori infection in more than 90% of the children was reported [19].

- Eradication failures in children are mostly due to noncompliance because of adverse effects or resistance to metronidazole and clarithromycin. Adverse effects can bereduced by probiotic supplementation such as Lactobacillus GG. If treatment fails,

antimicrobial sensitivities can be helpful in selecting antibiotics. Stool antigen testing may also have a role in predicting H pylori antibiotic

resistance. Reinfection after successful eradication of H pylori is uncommon in developed countries.

Diet

Foods such as berry juice and some dairy products may have modest bacteriostatic effect on H pylori.

Two randomized, placebo-controlled trials evaluated the effect of probiotic food as an adjuvant to the standard triple therapy for eradication of H pyloriinfection in children and showed conflicting results [20,21].

In a recent prospective study in adults, addition of vitamin C to an H pylori treatment regimen of amoxicillin, metronidazole, and bismuth can significantly increase H pylori eradication rate [22].

Medication

Antibiotics, beta-lactams

The beta-lactam used to treat patients with H pylori infection is stable in an acid environment, binds to proteins within bacterial cell walls, induces direct wall lysis, and inhibits cell-wall synthesis.

Amoxicillin

Dose: Adult: 250-500 mg/dose tid; not to exceed 2-3 g/d; Pediatric: 50 mg/kg/day divided bid; not to exceed 2-3 g/day

Antibiotics, macrolides

The macrolide used in the treatment of H pylori infection is stable in the gastric environment, enters the bacterial cell, binds to receptors on the ribosomal subunits, and inhibits bacterial protein synthesis.

Clarithromycin

Provides bacteriocidal activity against H pylori with antimicrobial spectrum similar to that of erythromycin but more stable in acid environment and has fewer adverse GI effects

Dose: Adult: 250 mg or 500 mg bid; administer with food; Pediatric: 15 mg/kg/day divided bid; not to exceed 500 mg bid; administer with food.

Antibiotics, anti protozoals

This antibiotic, used in the treatment of patients with H pylori infection, produces intracellular products that damage bacterial DNA.

Metronidazole

Metronidazole diffuses into all tissues well, is stable in an acidic pH environment, and provides bactericidal activity against H pylori.

Dose: Adult: 500 mg bid/tid; Pediatric: 20 mg/kg/day divided bid; not to exceed 500 mg bid.

Antibiotics, tetracyclines

Tetracyclines bind to ribosomal subunits and inhibit protein synthesis of susceptible bacteria. Use in pediatric patients should be restricted to children in whom other antibiotic regimens fail.

Tetracycline HCL

Bacteriostatic, but may be bactericidal at high concentrations.

Dose: Adult:

1-2 g/day divided q 6h; not to exceed 3 g/day ;to be administerd 1 h before or 2 h after meals. Pediatric: <8 years: Not recommended because of tooth staining and decreased bone growth>8 years: 25-50 mg/kg/day divided q 6h; not to exceed 3 g/day; to be administerd 1 h before or 2 h after meals.

H2-receptor antagonists

Receptors for H2 are located on the acid-producing parietal cells. Blocking histamine action suppresses gastric acid secretion.

Ranitidine

H2 antagonists prescribed for 8 wk, when most non– H pylori -associated ulcers heal. H2 blockers have no antibacterial effect; therefore, must be used with antibiotics to eradicate H pylori.

Dose: Adult: 150 mg/dose bid or 300 mg/dose qhs Alternative: 50 mg/dose IV/IM q 6-8h; Pediatric: Neonates: 4 mg/kg/day divided q 12h or 1.5 mg/kg/day IV divided 12h Infants and children: 6-9 mg/kg/day divided q8-12h or 2-4 mg/kg/day IV/IM divided q 6-8h Continuous infusion: Administer daily IV dose over 24 h.

Proton Pump Inhibitors

This class of drugs, which includes acid inhibitors more potent than the H2-receptor antagonists, blocks gastric acid secretion at the proton (Na+/H+ ATPase) pump, the final common pathway of secretion. This class is recommended as part of a drug regimen in symptomatic patients with H pylori infection. Similar to H2-receptor blockade, proton pump inhibitor (PPI) therapy alone does not eradicate H pyloriinfection; however, bacteriostatic activity against H pylori occurs.

Omeprazole

Potent blocker of gastric acid. Best administered just before first meal of day. Enteric-coated granules in cap ensure appropriate bioavailability

Dose: Adult: 20 mg/day once daily; Pediatric: 15-30 kg: 10 mg once daily>30kg: 20 mg once daily.

Lansoprazole

Potent blocker of gastric acid. Best administered just before first meal of day. Enteric-coated granules in the cap ensure appropriate bioavailability

Dose: Adult: 30 mg/day; Pediatric: 1 mg/kg/day.

Bismuths

Bismuth subsalicylate and bismuth subcitrate have complementary effects with most antimicrobials. Bismuth disrupts bacterial cell walls. Bismuth is particularly effective in lysing the cell wall of the organism when the organism is close to the gastric epithelium and relatively inaccessible to most antimicrobial agents.

Bismuth Subsalicylate

Lyses bacterial cell walls, prevents organism adhesion to epithelium, and inhibits urease.

Dose: Adult: 524 mg (2 tab or 30 mL) qid; not to exceed 8 doses

in 24 h Pediatric; 3-6 years: 5 mL (about 88 mg) or one third tab qid, 6-9 years: 10 mL (about 175 mg) or two thirds tab qid, 9-12 years: 15 mL (262 mg) or 1 tab (262 mg) qid.

Objective

Ornidazole is now being recommended alongwith amoxicillin, clarithromycin or tetracycline to eradicate Helicobacter pylori infection from the stomach. Current study showed that stomach specific delivery of these anti- Helicobacter pylori- drugs over a prolonged period of time may achieve adequate drug concentration in the echological niche of the bacteria under the submucus layer in the stomach wall, that may be more beneficial to eradicate the infection. The objective of the present study is to develop a sustained release gastroretentive tablet formulation of ornidazole in order to improve the efficacy of the delivery system in the eradication of Helicobacter pylori infection from the stomach. The gastric retention technique used in our study is based on gas generation and entrapment within the tablet that makes it buoyant in the gastric fluid.

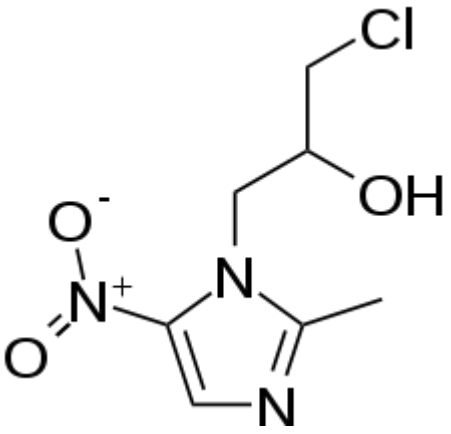
Drug Profile (API)

Ornidazole

Systematic (IUPAC) name:

1-chloro-3-(2-methyl-5-nitro-1H-imidazol-1-yl)propan-2-ol

Ornidazole is a drug that cures some protozoan infections. It is used by the poultry industry.It has been investigated for use in Crohn's disease after bowel resection.Ornidazole (ORN) is the nitroimidazole derivative. Chemically it is 1-chloro-3-(2-methyl-5 nitroimidazol-1-yl) propan-2-ol 1-(3-chloro-2-hydroxypropyl)-2-methyl-5- nitroimidazole [1,2]. It is used as anti infective and anti protozoal agent.



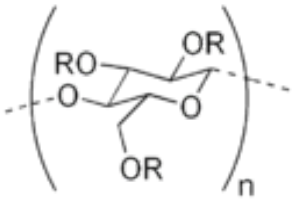
Excipients profile

HPMC

Hypromellose (INN), short for hydroxypropyl methylcellulose (HPMC), is a semisynthetic, inert, viscoelastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.

As a food additive, hypromellose is an emulsifier, thickening and suspending agent, and an alternative to animal gelatin. Its Codex Alimentarius code (E number) is E464.

Hypromellose



R = H or CH_3 or $CH_2CH(OH)CH_3$

Hydroxypropyl methylcellulose; hydroxypropyl methyl cellulose; HPMC; E464

Hypromellose is a solid, and is a slightly off-white to beige powder in appearance and may be formed into granules. The compound forms colloids when dissolved in water. Although non-toxic, it is combustible and can react vigorously with oxidising agents.

Hpmc k4m

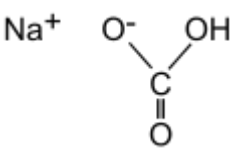
1.methoxyl:19.0-24.0%
2.hydroxypropxy:4.0-12.0%

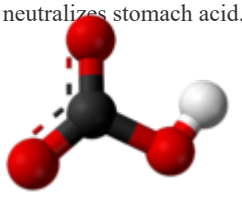
Product CharacteristicsAppearance: HPMC is a white to light yellow powder or granular product.Solubility: HPMC is nearly insoluble in anhydrous ethanol, ethyl ether and acetone It is swelled in cold water to form a transparent or a slight cloudy solution. HPMC can be dissolved into some organic solvents and also in water-organic solvent mixed solvents. Fineness(Graininess):Theoversizeproductabove100meshshouldnotexceed 5.0%. With reduction of methoxyl groups content, HPMC is increased in gelling temperature and decreased in water solubility and surface activity. Purpose of Application multipurpose additive for pharmaceutical, can be functioned as thickener, dispersant, emulsifier, film forming agent, etc. It is used in tablets for dressing and binding to improve solubility of the drugs and reinforce tablets' water prevention function. It can also be utilized as mixed suspending agent, additive for eye drops, sustainedrelease agent, etc. HPMC can be widely used in the fields of detergent and cosmetics industries as thickener and emulsion stabilizer to improve rheologic property. PMC can be directly applied to food not only as emulsifier, binder, thickener or stabilizer, but also as packing material.

$NaHCO_3$

Sodium bicarbonate ($NaHCO_3$) is a white crystalline powder commonly known to as baking soda. It is classified as an acid salt, formed by combining an acid (carbonic) and abase (sodium hydroxide), and it reacts with other chemicals as a mild alkali. At temperatures above 300°F (149°C), sodium bicarbonate decomposes into sodium carbonate (a more stable substance),water, and carbon dioxide.

Sodium bicarbonate is an antacid that neutralizes stomach acid.





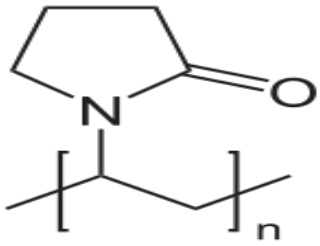
Use:

Sodium bicarbonate is used in an aqueous solution as an antacid taken orally to treat acid indigestion and heartburn.[12] It may also be used in an oral form to treat chronic forms of metabolic acidosis such as chronic renal failure and renal tubular acidosis. Sodium bicarbonate may also be useful in urinary alkalinization for the treatment of aspirin overdose and uric acid renal stones. It is used as the medicinal ingredient in gripe water for infants.

PVP

PVP is soluble in water and many organic solvents and it forms hard, transparent, glossy film. It is compatible with most inorganic salts and many resins. PVP stabilizes emulsions, dispersions and suspensions.

PVP - K30



Molecular formula:$(C_6H_9NO)_n$

Description:

PVP exists as powder or aquous solution.

It can dissolve in water and a variety of organic solvent.

It has good hygroscopicity, film-forming capability, complexing ability and physiology compatibility.

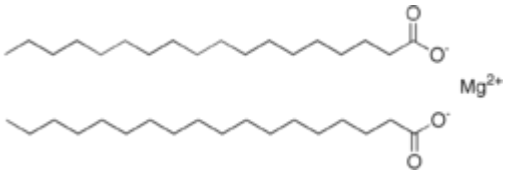
Povidone k30 is a new and excellent pharmaceutical excipient. It is mainly used as binder for tablet, dissolving assistant for injection, flow assistant for enzyme and heat sensitive drug, coprecipitant for poorly soluble drugs, lubricator and antitoxic assistant for eye drug. PVP works as excipients in more than one hundreds drugs.

Magnesium stearate

Magnesium stearate, also called octadecanoic acid, magnesium salt, is a white substance which is solid at room temperature. It has the chemical formula $Mg(C_{18}H_{35}O_2)_2$. It is a salt containing two equivalents of stearate (the anion of stearic acid) and one magnesium cation (Mg^{2+}).

Magnesium stearate is a major component of "bathtub rings". When produced by soap and hard water, magnesium stearate and calcium stearate both form a white solid insoluble in water, and are collectively known as "soap scum".

Magnesium stearate



Magnesium octadecanoate

Uses

Magnesium stearate is often used as a diluent in the manufacture of medical tablets, capsules and powders. In this regard, the substance is also useful, because it has lubricatingproperties, preventing ingredients from sticking to manufacturing equipment during the compression of chemical powders into solid tablets; magnesium stearate is the most commonly used lubricant for tablets. Studies have shown that magnesium stearate may affect the release time of the active ingredients in tablets, etc., but not that it reduces the over-all bioavailability of those ingredients. As a food additive or pharmaceutical excipient, its E number is E470b.

Talc

Three pieces of Talc.

General	
Category	Silicate mineral
Chemical formula	$Mg_3Si_4O_{10}(OH)_2$

Talc is a mineral composed of hydratedmagnesiumsilicate with the chemical formula H2Mg3(SiO3)4 or Mg3Si4O10(OH)2. In loose form, it is the widely-used substance known as talcum powder. It occurs as foliated to fibrous masses, its crystals being so rare as to be almost unknown. It has a perfect basal cleavage, and the folia are non-elastic, although slightly flexible. It is the softest known mineral and listed as 1 on the Mohs hardness scale.

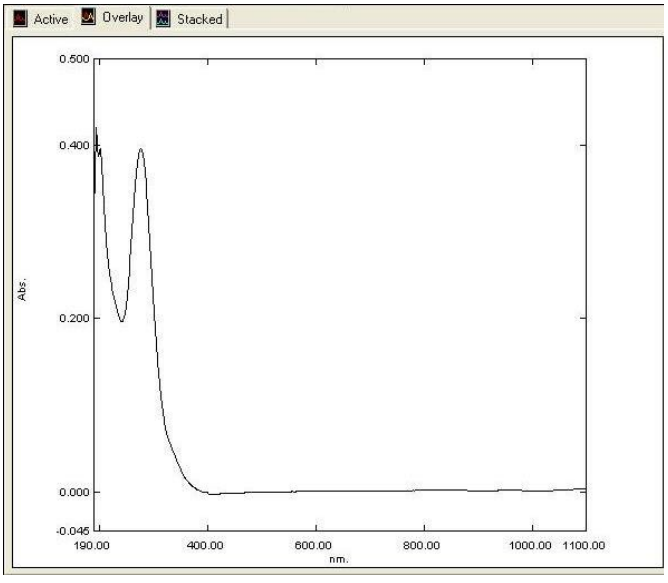
Uses

Talc is used in many industries such as paper making, plastic, paint and coatings, rubber, food, electric cable, pharmaceuticals, cosmetics, ceramics, etc. It is often used for surfaces of lab counter tops and electrical switchboards because of its resistance to heat, electricity and acids. Talc finds use as a cosmetic (talcum powder), as a lubricant, and as a filler in paper manufacture. Talc is used in baby powder, an astringent powder used for preventing rashes on the area covered by a diaper (see diaper rash).

Experimental part

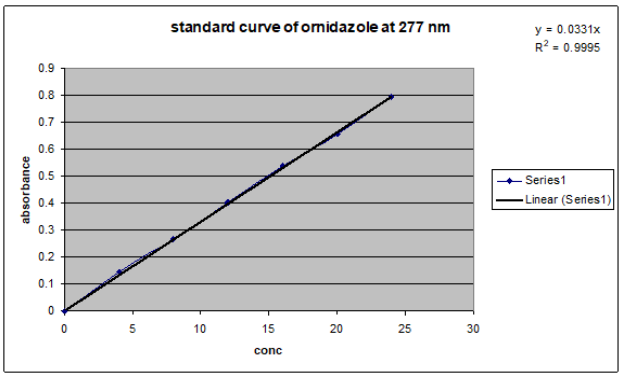
Preparation of standard curve:

Method: a stock solution of ornidazole in 0.1N HCl acid was prepared with the conc. of 1mg/ml. Then, six standard solutions with conc of 4, 8, 12, 16, 20 and 24 µg/ml respectively were prepared from the stock solution and their absorbance were measured at 293 nm by double beam UV-Visible Spectrophoyometer (Pharmaspec 1700,Shimazdu, Japan). Absorbances were then plotted against conc and a standard curve was obtained. The equation of the curve was y= 0.0331x and R2 value 0.9995.



Peak Pick

No.	P/V	Wavelength nm.	Abs.	Description
1	↑	326.00	0.408	
2	↑	293.00	1.094	
3	↑	226.00	0.619	
4	↑	201.00	0.466	
5	↓	451.00	0.002	
6	↓	320.00	0.401	
7	↓	263.00	0.302	
8	↓	205.00	0.458	



Formula of the tablets:

The formulation was designed using 23 full factorial design. HPMC K4M, HPMC 100M and NaHCO3 were taken as independent variables. The formula of 8 batches were given in following table.

Formulation code	Average weight	Std. dev.
F_1	779.6	3.714835
F_2	819.8	3.193744
F_3	848.6	6.228965
F_4	810.2	4.32435
F_5	908.8	8.348653
F_6	861.4	3.781534
F_7	826.6	4.669047
F_8	870.4	5.813777

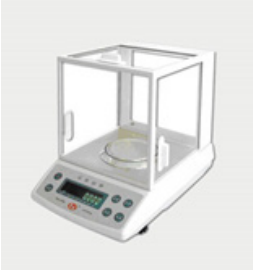
Preparation of floating tablet:

The floating matrix tablet ofornidazole were prepared by wet granulation method. At first, drug, HPMC K4M, HPMC 100M, and NaHCO3 were mixed well by geometric diluton method using pestle and mortar. Then this mixture were moistened by ethanolic solution of PVP. Then granules were prepared by passing the mass through a 22 no sieve and dried at 50°C for 30 mins. The dried granules were again passed through the same sieve and talc and magnesium stearate were mixed. Finally the granules were compressed into tablet using 10mm die-punch.

Formulation code	Ornidazole (mg)	HPMC K4M (mg)	HPMC 100M (mg)	$NaHCO_3$ (mg)	PVP K30 (mg)	Magnesium Stearate (mg)	Talc (mg)
F_1	500	100	30	80	50	10	10
F_2	500	100	30	120	50	10	10
F_3	500	100	60	120	50	10	10
F_4	500	100	60	80	50	10	10
F_5	500	150	60	120	50	10	10
F_6	500	150	60	80	50	10	10
F_7	500	150	30	80	50	10	10
F_8	500	150	30	120	50	10	10

Evaluations:

1. Weight variation test: 5 tablets in each batch were weighed accurately and then average weight and standard deviation was calculated.



Content uniformity test:

Three tablets were assayed in each formulation. Then average drug content as the % of label claimed were calculated. (Spectrophotometric assay procedure was followed, standard curve equation was used for this perpouse).

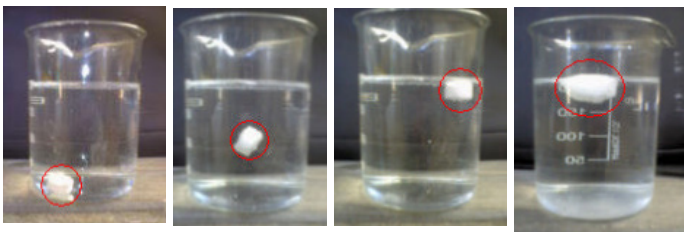
Formulation code	Average drug content as % of Label claimed	**Std. dev.**
F_1	100.1667	2.107922
F_2	99.19	1.707132
F_3	100.2033	2.942352
F_4	99.66667	3.785939
F_5	97.54333	1.065004
F_6	102.57	2.700389
F_7	101.45	3.602041
F_8	100.3233	3.473404

Hardness and friability test:

Hardness of the tablets were measured by Monsanto hardness tester. Friability test was performed by placing one tablet from each formula in Roche type friabilator and rotating it in 25 rpm speed for 4 min. Then the tablet was reweighed and % friability was calculated from the following formula: % friability = (wo- w)100/wo.

Formulation code	Hardness (kg/ cm^2)	% friability
F_1	4.5	0.11
F_2	5.5	0.13
F_3	5	0.02
F_4	5.25	0.05
F_5	6	0.01
F_6	5.5	0.10
F_7	5	0.09
F_8	5.5	0.03

In vitro floating test:



In vitro floating test was performed by placing tablet in 0.1N HCl acid in a 250 ml beaker. The floating lag time and total floating time were noted.

In vitro drug release study:

This test was performed using USP Dissolution test apparatus type 1 (basket type). 900ml 0.1N HCl acid was used as dissolution medium, the temperature was maintained at 37°C±0.5°C and the speed of the rotation of the basket was maintained at 50±2 rpm. 5ml sample was withdrawn from the dissolution medium at predetermined time points and 5ml fresh buffer was added to it each time. The study was done over 16 hr period. The samples were then analyzed spectrophotometrically after suitable dilution using standard curve equation. Finally cumulative percent drug release were calculated at different time points. The

dissolution data were analyzed by fitting them into different kinetic model to understand the proper kinetic of drug release and mechanism of drug release from the tablet.

Formulation code	Floating lag time (FLT) (min)	Total floating Time (TFT) (hr)
F_1	5	>8
F_2	1	>8
F_3	4	>8
F_4	5	>8
F_5	3	>8
F_6	10	>8
F_7	4	>8
F_8	2	>8

In vitro drug release study:

This test was performed using USP Dissolution test apparatus type 1 (basket type). 900ml 0.1N HCl acid was used as dissolution medium, the temperature was maintained at 37°C±0.5°C and the speed of the rotation of the basket was maintained at 50±2 rpm. 5ml sample was withdrawn from the dissolution medium at predetermined time points and 5ml fresh buffer was added to it each time. The study was done over 16 hr period. The samples were then analyzed spectrophotometrically after suitable dilution using standard curve equation. Finally cumulative percent drug release were calculated at different time points. The dissolution data were analyzed by fitting them into different kinetic model to understand the proper kinetic of drug release and mechanism of drug release from the tablet.

CPR

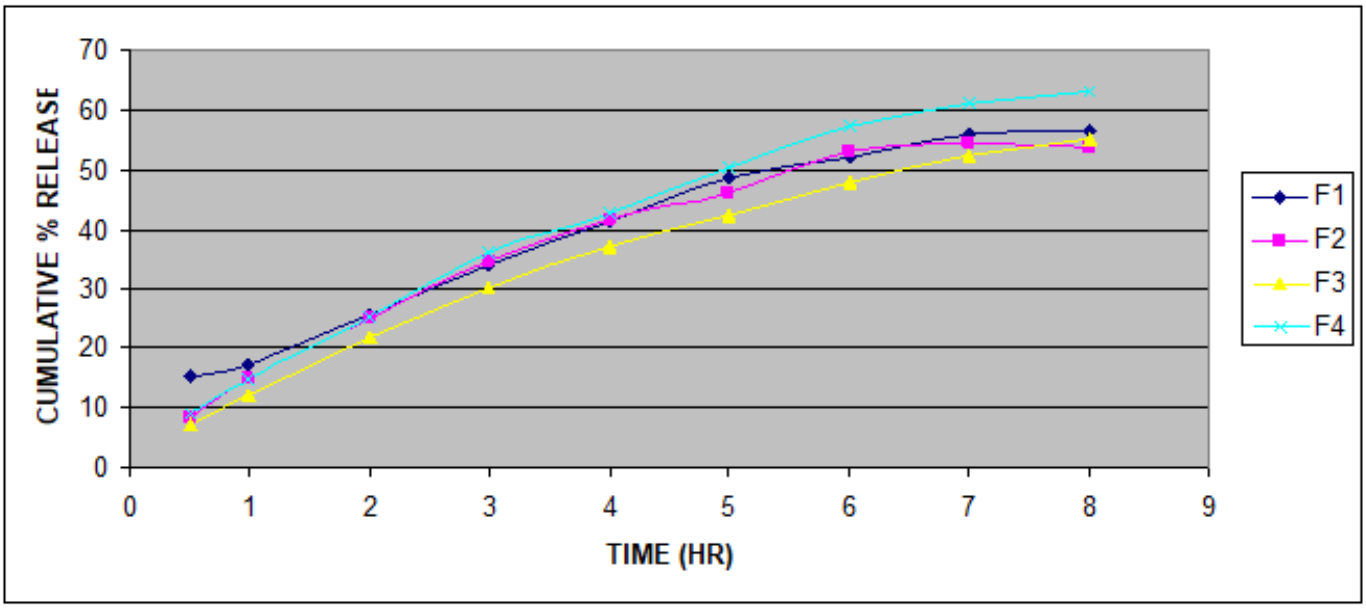
Time(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	15.0906	8.42900	7.20543	8.83685	1.22356	1.49546	6.11782	6.38972
1	17.4856	14.8655	12.2756	14.7318	3.54154	4.49471	9.00679	9.41616
2	25.6034	24.8723	21.9962	25.2817	11.0385	12.5407	15.9901	16.2658
3	34.0377	34.5264	30.2749	35.8897	21.2960	19.5438	22.6042	21.3859
4	41.2945	41.5143	37.2394	42.4773	27.9395	28.2167	28.9826	26.6699
5	48.4546	45.9569	42.3383	50.3240	33.6676	33.6744	34.7160	31.5747
6	51.8466	53.0060	47.7364	57.2613	40.5143	39.0256	39.5287	36.6419
7	55.9358	54.3829	52.2114	60.8368	45.2228	47.5324	43.8232	42.4161
8	56.3753	53.7265	54.9426	62.93505	51.72356	53.63822	47.46073	45.63822

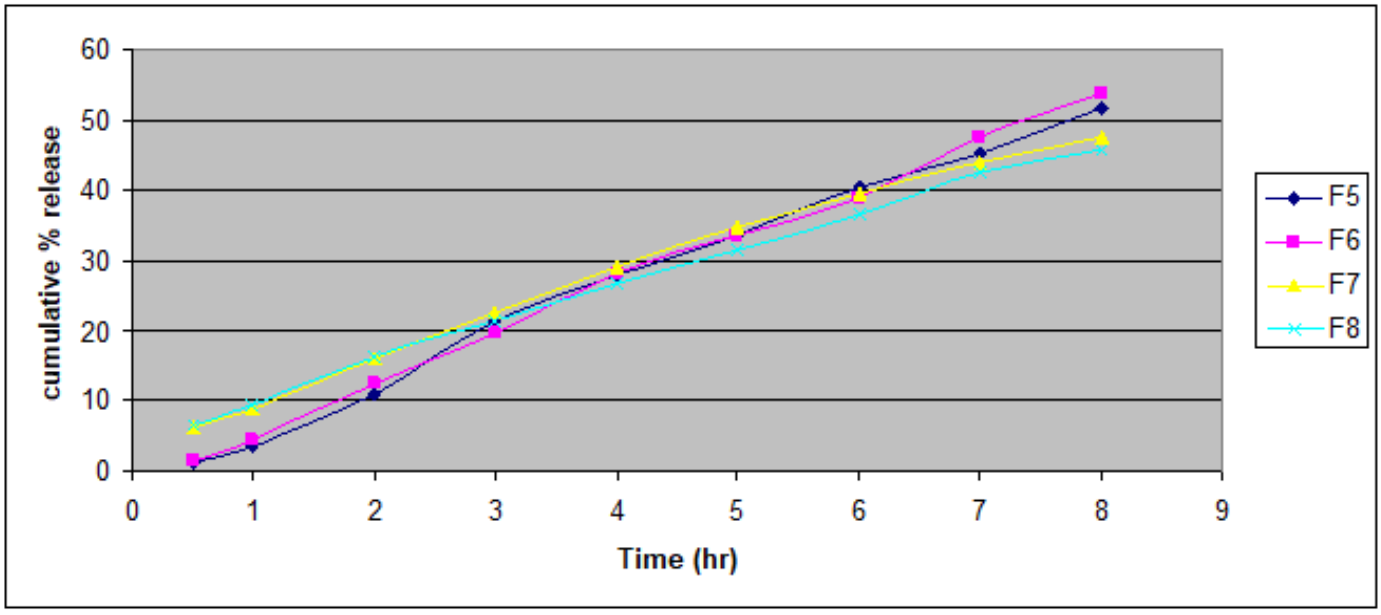
Discussion: the study revealed that floating lag time greatly depends on the amount of sodium bicarbonate.

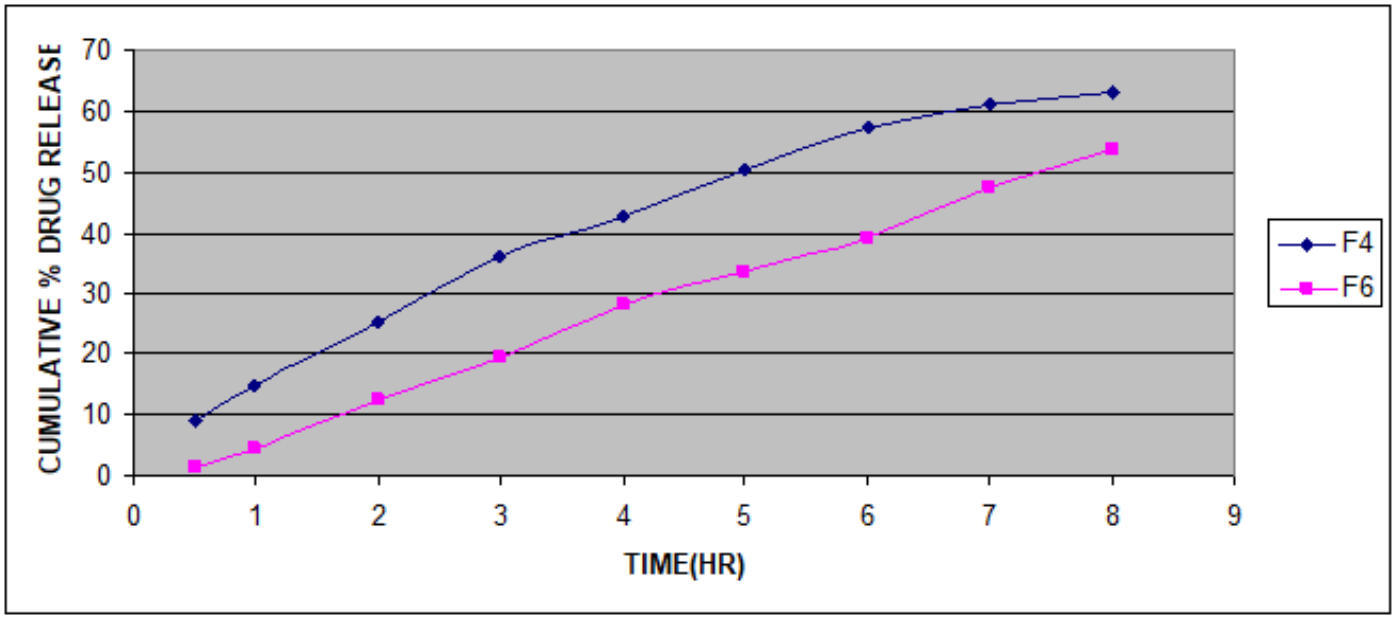
The invitro release study showed that HPMC K4M retarded the drug release more than that of HPMC 100M, sodium bicarbonate has no significant effect on drug release. HPMC K4M has more water uptake capacity and forms a gel around the tablet surface more likely than HPMC 100M. The analysis of dissolution data revealed that drug release occurs following peppas-korsemeyer kinetic and by Non-Fickian anomalous diffusion mechanism. Initially a gel layer of hydrophilic polymer is formed around the tablet and drug diffuses through this barrier. The gel barrier gradually propagate towards the interior of the tablet. The viscosity of outer gel layer gradually decreases and therefore undergoes erosion. The drug release mechanism combines both erosion and diffusion.

value

FORMULA CODE	Zero Order	First order	Higu-chi	hixon Crowell	R2 Peppas R2	korsmeyer n	Best model
F1	0.9617	0.8984	0.9854	0.9757	0.9801	0.5289	Higuchi
F2	0.9256	0.8001	0.9812	0.9468	0.9862	0.6918	peppas
F3	0.9706	0.8382	0.9981	0.9881	0.9957	0.7462	Higuchi
F4	0.9651	0.8425	0.9947	0.9855	0.9957	0.7305	peppas and Higuchi
F5	0.9925	0.7959	0.9854	0.9978	0.9853	1.3588	HC
F6	0.9975	0.8114	0.9791	0.9961	0.9896	1.2714	zero order
F7	0.9903	0.8888	0.9911	0.9974	0.9965	0.7705	HC
F8	0.9962	0.9042	0.9865	0.9988	0.9973	0.7247	HC and peppas







Comparision of the dissolution data between F4 and F6 to show the effect of HPMC K4M and hpmc 100M on the drug release.

Conclusion

In this work, a sustained release gastroretentive tablet of ornidazole was aimed to develop. The study showed that the tablets of F8 formula took minimum floating lag time and had most sustained release capacity. Therefore, F8 was the best formulation among the 8 different batches. For future work, dissolution study over more extended period of time and in vivo gastroretentive capacity as well as in vivo eradication efficacy may be carried out to place it in the market.

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