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To Design Famotine And Clindamycin Gastro Re-tentive Floating Tablet

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ABSTRACT

HPMC K4M, HPMC K15M, and HPMC K100M polymers are used in this study to make floating tablets of famotidine hydrochloride. Drug Delivery systems that are floating in the stomach have a lower bulk density than gastric fluids, therefore they stay buoyant in the stomach for a lengthy period of time without impacting gastric emptying rate. In the treatment of gastroesophageal reflex disease (GERD) and peptic ulcer (PUD). Famotidine is a histamine H2 receptor antagonist (GERD). Famotidine is an excellent option for a floating drug delivery system because of its short half-life, brief time in the stomach, and repeated doses. Melt granulation technique was used to make famotidine floating tablets using HPMC K4M, HPMC K15M, and HPMC K100M. In vitro buoyancy, drug polymer compatibility (IR Research), weight fluctuation, hardness, friability, thickness, drug content and invitro dissolution experiments were all performed on the floating tablets. Using in vitro buoyancy and dissolvability experiments, we were able to establish that the micromeritic characteristic were excellent. HPMC K100M-based formulation F4 has an excellent in vitro buoyancy lag time and floating time, and in vitro dissolution investigations demonstrate a 96.78 percent release for 12 hours. As a result of the findings of this research, it can be concluded that famotidine floating tablets provide the potential for longest- term drug delivery and a consequent reduction in dosage frequency.

INTRODUCTION

A **tablet** it is also called as a **pill** is a pharmaceutical oral dosage form or solid unit dosage form. Tablets may be defined as the solid unit dosage form of medication with suitable excipients . It comprises a mixture of active ingredients and excipients, usually in powder form, that are pressed or compacted into a solid dose. The main advantages of tablets are that they ensure a consistent dose of medicine that is easy to consume.

Tablets are prepared either by moulding or by compression . The excipients can include diluents , binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tabletting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavours to enhance taste; and pigments to make the tablets visually attractive or aid in visual identification of an unknown tablet. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment, or to enhance the tablet's appearance.[1]

Medicinal tablets were originally made in the shape of a disk of whatever colour their components determined, but are now made in many shapes and colours to help distinguish different medicines. Tablets are

often imprinted with symbols, letters, and numbers, which allow them to be identified, or a groove to allow splitting by hand. Sizes of tablets to be swallowed range from a few millimetres to about a centimetre.

The compressed tablet is the most commonly seen dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. A tablet can be formulated to deliver an accurate dosage to a specific site in the body; it is usually taken orally, but can be administered sublingually , buccally , rectally or intravaginally . The tablet is just one of the many forms that an oral drug can take such as syrups , elixirs , suspension , and emulsions .[2]

A multiple unit oral floating drug delivery system of famotidine was developed to prolong gastric residence time, target stomach mucosa and increase drug bioavailability. Drug and polymer compatibility was studied by subjecting physical mixtures of drug and polymers to differential scanning calorimetry.

Gastroretentive drug delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract. A modified release drug delivery system with prolonged residence time in the stomach is of particular interest for drugs- acting locally in the stomach; having an absorption window in the stomach or in the upper part of small intestine; those unstable in the intestinal or colonic environments; or those having low solubility at high pH values.[3]

To formulate a successful gastroretentive drug delivery system, several techniques are currently used such as floating drug delivery system, low density systems, raft systems incorporating alginate gel, bioadhesive or mucoadhesive systems, high density systems, superporous hydrogel and magnetic system. Among these, the floating dosage forms have been most commonly used.

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and control of the fluctuation in plasma drug concentration. [4]

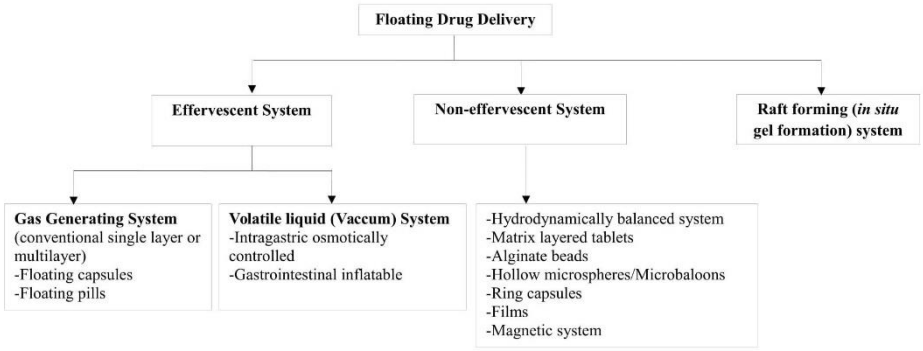
Oral route is the most preferred route of drug delivery due to ease of administration and greater patient compliance, although studies revealed that this route is subject to two physiological influences, a short gastric residence time (GRT) and variable gastric emptying time (GET), which may lead to unpredictable bioavailability and times to achieve peak plasma levels. Furthermore, the brief GET in humans, which normally averages 2-3 h through the major absorption zone (stomach and upper part of the intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficacy of the administered dose. Thus, control of placement of a drug delivery system in a specific region of the gastro intestine (GI) tract offers numerous advantages like improved bioavailability and therapeutic efficacy, local delivery of drug and possible reduction of dose size. All these considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities.

Gastroretentive systems can remain in the gastric region for several hours and significantly prolong the gastric residence of the drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, improve solubility of drugs that are less soluble in a high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine.[5]

Floating tablet is a class of gastroretentive drug delivery system. Gastroretentive systems are able to increase residence time of dosage forms in the stomach there by increase the bioavailability of drugs with narrow absorption window, drugs with less water solubility in alkaline pH of small intestine or drugs with poor stability in the intestinal or colonic environment. The important point in the development of oral controlled release dosage forms is not just to prolong the delivery of the drug more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal tract unit all the drug is released for desire period of time. Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose. [6]

Floating drug delivery systems (FDDS) are invented to retain the drug in the stomach and applicable for drugs with poor solubility and low stability in intestinal fluids. The basis behind FDDS is making the dosage form

less dense than the gastric fluids to make it float on them. FDDS are hydro-dynamically controlled low-density systems with sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The residual system is emptied from the stomach with the release of the drug. This results in enhanced gastric residence time and good control over plasma drug concentration fluctuations. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. Prolonging the gastric retention of a delivery system is desirable for achieving the greater therapeutic efficacy of the drug substance under certain circumstances. For example, drugs which show better absorption at the proximal part of the gastrointestinal tract and drugs with low solubility and get degraded in alkaline pH found efficient in prolonging gastric retention. In addition, for sustained drug delivery to the stomach and proximal small intestine in treating certain ulcerative conditions, prolong gastric retention of the therapeutic moiety and hence offer numerous advantages including improved bioavailability and therapeutic efficacy with reduction of dosing frequency . Fig. describes the classification of FDDS with consideration of its physiochemical behavior and appearance. [7]



CLASSIFICATION:

A. Effervescent FDDS

1. Gas generating system
2. Volatile liquid containing system

B. Non-Effervescent FDDS

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

C. Raft forming system

Effervescent FDDS :

This system makes use of a floating chamber filled with water, vacuum, air, or inert gas. CO2 which is formed as a result of an effervescent reaction between the organic acid (citric acid) and the carbonate / bicarbonate salts can be introduced into the floating chamber. Such a system uses matrix prepared with swellable polymers such as chitosan-like polysaccharides, effervescent materials such as citric acid, sodium bicarbonate, and tartaric acid, or chambers containing a liquid that gasifies at the body temperature.

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

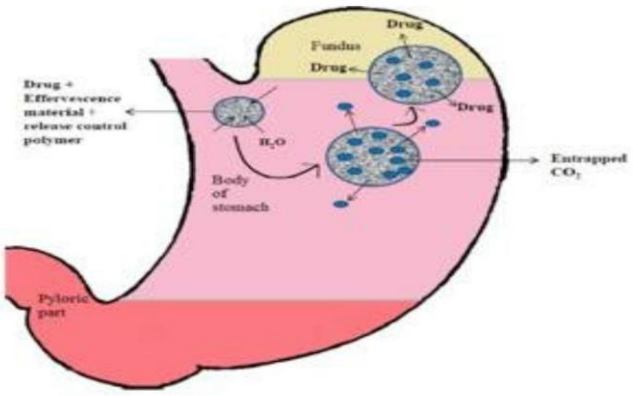


Fig. GRDDS based on effervescence

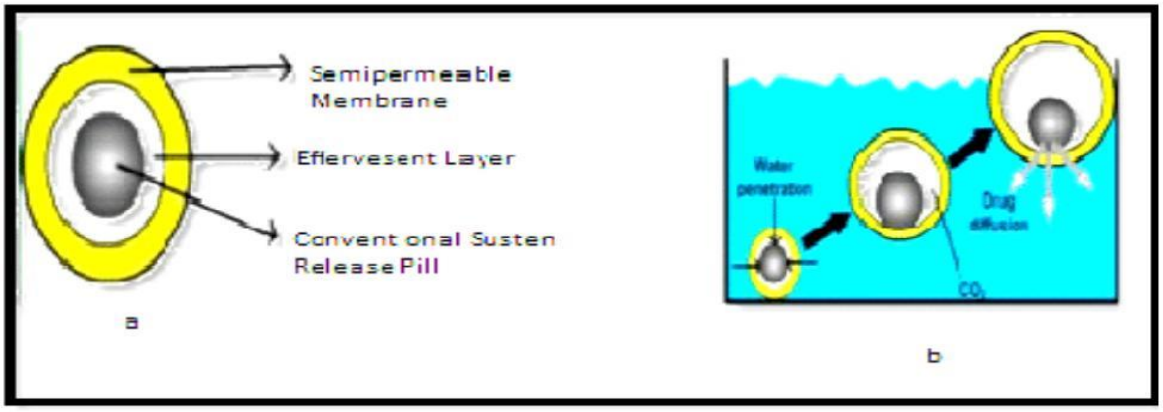


Fig. Multiple – unit oral drug delivery system

Gas generation system:

This buoyant delivery system uses effervescence reaction between citric acid / tartaric acid and carbonate / bicarbonate salts to release CO2 which further reduces its specific gravity and makes it float over chime.

Low-density FDDS is based on the release of co_2 upon contact with gastric fluids after oral administration. The materials are formulated in such a way that after entering in the stomach, co_2 is librated due to reaction with acidic gastric content and which get entrapped in the gel-based hydrocolloid (fig.2). It produces an upward motion of the dosage form and maintains its buoyancy. Ultimately it causesa decrease in specific gravity of dosage form and hence resulting into a float on the chime. The co_2 generating components are mixed within the tablet matrix in a single layer or multi-layered form to produce gas generating mechanism in hydrocolloid layer, and the drug in the other layer results into a sustained release effect.

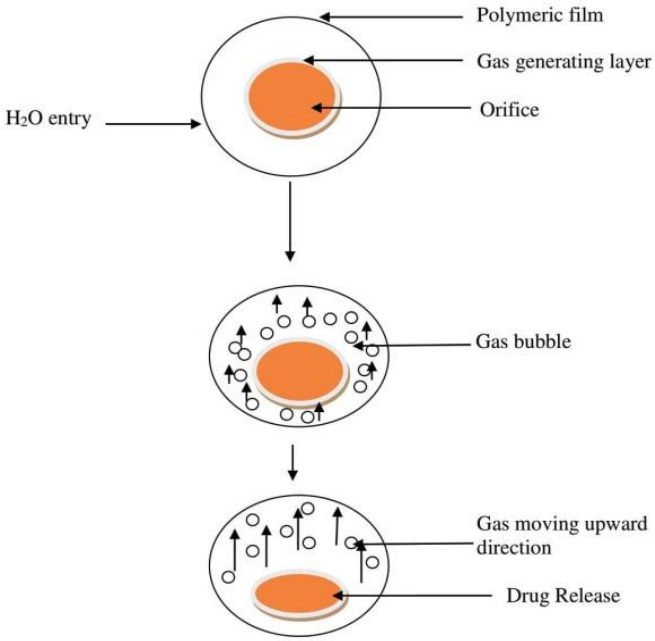


Fig.2: Mechanism of floatation via CO_2 liberation

Volatile liquid storage system:

These contain an inflatable chamber consisting of a liquid, e.g. cyclopentane, ether, which gasifies at body temperature to induce inflation of the chamber in the stomach. The system consists of two chambers the first chamber consisting of the drug, and the volatile liquid in the second chamber.

This is an osmotically controlled floating system in which a device comprised of a hollow deformable unit in convertible collapsed form. Housing would be attached to its deformable unit and internally divided into a first and second chamber separated by an impermeable, pressure sensitive movable unit. The first chamber usually contains an active drug, while the second a volatile liquid, such as cyclopentane or ether get vaporized at a physiological temperature to produce a gas, enabling the drug reservoir to float. The unit gets expelled from the stomach, with the help of bioerodible plug that allowed the vapour to escape.

Non-Effervescent FDDS :

Non-Effervescent Floating Drug Delivery Systems comprises a gel-forming (or) swellable cellulose type of hydrocolloids made up of polysaccharide along with matrix forming polymers like polycarbonate, polymethacrylate ,and polystyrene. The routine formulation method involves the mixing of the drug with gel forming hydrocolloids that swell in contact with gastric fluid upon oral administration and maintains the integrity of shape and a bulk density barrier, the air trapped by swollen polymer confer buoyancy to the dosage forms.

In GI tract, the non-effervescent FDDS is based on the mechanism of polymer swelling or bioadhesion to the mucosal layer. The excipients most frequently used in non-effervescent FDDS are:

- Hydrophilic gums,
- Gel forming or highly swellable cellulose type hydrocolloids
- Polysaccharides and matrix forming materials such as polymethacrylate, polycarbonate, polystyrene, polyacrylate, as well as bioadhesive polymers such as Carbopol and Chitosan.

Colloidal gel barrier systems / Single layer floating tablets:

Such systems contain a high degree of one or more gel forming, cellulose type hydrocolloids, polysaccharides, and polymers forming matrix, which are extremely swellable.

This system prolongs gastric retention time and maximizes the amount of drug that reaches its absorption site in the solution form. It essentially contains drug with gel-forming hydrocolloids to remain buoyant on the stomach content. Such a system incorporates one or more gel-forming cellulose type hydrocolloid e. g. hydroxypropylmethylcellulose (HPMC), polysaccharides and matrix forming polymers such as polycarbophil,

polystyrene, and polyacrylate. Upon contact with gastro-Intestinal (GI) fluid, the hydrocolloid in the system hydrates to generate a colloid gel barrier to its surrounding.

Bi-layer floating tablets:

A bi-layer tablet comprises of two layers with first layer is the immediate release layer, which releases the initial dose from the system while the other is the sustained release layer which absorbs the gastric fluid, creating an impermeable colloidal gel barrier on its surface and retaining a bulk density of less than 1.

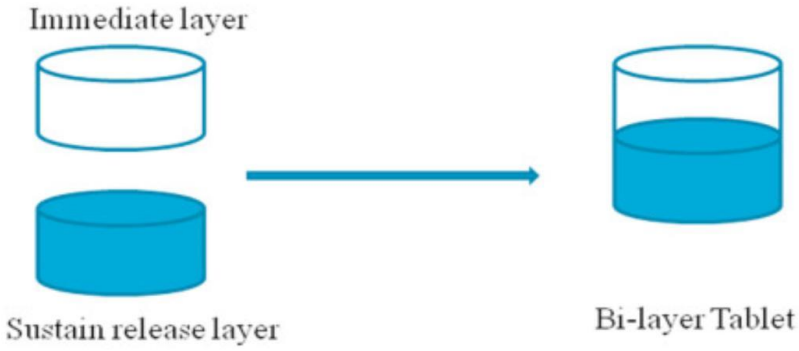


Fig. Bilayer Tablet

Micro porous compartment systems:

This technology is based on a drug reservoir being encapsulated within a micro porous compartment with apertures along its top and bottom walls.

This technology incorporates the encapsulation technique of a drug reservoir inside a microporous compartment along with pores at top and bottom walls. The peripheral wall of the drug reservoir compartment is completely sealed to prevent any direct contact of the gastric surface with the undissolved drug. In the stomach, the floatation chamber composed of entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, to the extent that it prevents theirs exist from the drug and carrier the dissolved drug for continuous transport across the intestine for absorption

Multi particulate system: Floating beads / Alginate beads:

Multi-particulate drug delivery systems are often oral dosage types consisting of a multiplicity of small discrete units.

Multi-unit floating dosage forms have been developed from calcium alginate spherical beads of about 2.5 mm in diameter and can be fabricated by adding sodium alginate solution into aqueous solution of calcium chloride, resulting in the precipitation of calcium alginate, the beads are further separated, snap-frozen in liquid nitrogen and freeze-dried at 400 °C for 24 h, leads to generation of a porous system. This fabricated system would maintain a floating force for over 12 h and these floating beads provide a longer residence time of more than 5.5 h.

Micro balloons/Hollow microspheres:

Hollow microspheres, also known as micro balloons when immersed in aqueous media they were found to float in vitro for 12 hrs.

Hallow microspheres are considered as a most efficient buoyant system. It is composed of central hallow space inside the microsphere. Hallow microsphere is loaded with a drug in their outer polymer shelf are fabricated by a novel solvent Diffusion method for emulsion.

Raft Forming System :

For the delivery of antacid and other medications for gastro-infection and gastro intestinal disorders, a Raft forming systems are mostly considered. Upon contact with gastric fluid the gel forming solution swells and creates a viscous compact gel containing an entrapped CO2 bubbles forming raft layer on top of gastric fluid that gradually releases the drug substance into the stomach.[8,9]

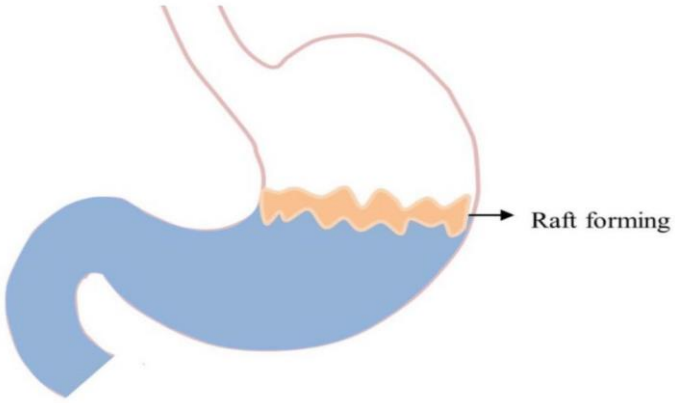


Fig. GRDDS based on Raft Forming System.

Advantages of floating drug delivery system

Floating dosage systems are delivery systems with gastric retentive behavior and offer several advantages in drug delivery. Some of these include:

1. Simple and conventional technique for formulation.
2. Site-specific drug delivery.
3. Controlled delivery of drugs.
4. Delivery of drugs for residual action at a specific site in the stomach.
5. Improved drug absorption with increased GRT and excess duration of contact of dosage regimen at its target site.
6. Minimizing irritation of GIT mucosa by the drugs with slow release rate. Acidic drug substances like aspirin cause irritation to gastric mucosa as it comes in contact. Hence HBS formulation would be beneficial in administration of aspirin and other similar drugs. Administration of prolonged release floating dosage forms, tablet or capsules, causes dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid before getting absorbed in the small intestine with emptying stomach contents. Hence it is expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
7. When there would be vigorous intestinal movement with short transit time, it might result in a certain type of diarrhea hence poor absorption is expected. Under such conditions, it is advantageous to maintain the drug in floating condition in the stomach for better efficacy.
8. In treating gastroesophageal reflux disorders (GERD).
9. Ease of administration with higher patient compliance.

The floating drug delivery system also carries certain disadvantages which limit its applicability.[9]

Disadvantages of floating drug delivery system

1. The major disadvantage of a floating system is due to the necessity of a sufficient level of gastric fluids to float without a sink. However, this limitation can be overcome by coating the dosage form with bio adhesive polymers that easily adhere to gastric mucosa.
2. The drugs those get significantly absorbed throughout gastrointestinal tract, with significant first-pass metabolism, are desirable candidate predominantly.
3. Certain drugs present in the floating system may causes irritation to gastric mucosal linings.
4. Gastric emptying of floating systems may occur at random and highly dependent on its dimensions. Therefore, patients should not have dosage prior going to bed. [9]

Limitations of floating drug delivery system

1. FDDS need to be administered after the meal but the residence and emptying time of drugs depends upon the digestive state which affects its absorption.
2. Floating ability depends on the hydration state of the dosage form. It is necessary of administration of water intermittent (a tumbler full, every 2 h) to keep these tablets floating *in vivo*.
3. Floating ability of drug in the stomach depends upon the person being positioned.

4. Drugs with solubility or stability problems with the gastric fluid are not a suitable candidate for FDDS.

5. Certain drugs though readily get absorbed in the stomach with successful first pass metabolism are not suitable as slow gastric emptying may lead to the reduced systemic bio-availability e. g. Nifedipine.[9]

Application of floating drug delivery system

1. FDDS are claimed for the increased efficacy of drugs as recent studies show that the administration of Diltiazem floating tablets twice a day would be more effective compared to normal tablets in hypertensive patients.

2. In case of Parkinson patient, FDDS is effective in absorption of the drug over a period of 6-8 h and maintained substantial plasma concentration.

3. FDDS is site-specific drug delivery: These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine, e. g., Riboflavin and Furo-semide.

4. FDDS served as an excellent drug delivery system in the eradication of Helicobacter pylori, blamed for chronic gastritis and peptic ulcers.

5. FDDS are perfect HBS dosage form to provide better delivery of drugs and reduced its GI side effects.[9]

Bilayer Tablet :

Bilayer tablets are the medicines which consist of two same or different drugs combined in a single dose for effective treatment of the disease. The aim of this review is to reveal the challenges that appear during the preparation of bilayer tablets, and also propose solutions for these challenges. Moreover, types such as single side press, double side press, and bilayer tablet displacement press along with applications, pros, and cons of bilayer tablets are mentioned to better understand the bilayer tablet.

Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize the area of contact between two layers.

The development of sustained or controlled drug delivery systems has got momentum over the past decade due to immense focus on the marketing of new drug molecules as the combination of these new drug molecules has increased to counter multiple diseases that require different dosage regimens. Bilayer tablet has patient compliance and is beneficial for either sequential release of two drugs in combination or sustained and immediate release of the same drug one as initial and other as a maintenance dose. Therefore, this report aims to shed light on the significance of bilayer tablets in the drug delivery system and to counter challenges that are faced in its manufacturing. Besides, numerous techniques for its formation and various bilayer tablets use for different diseases are also analyzed in this article.[10]

Advantages of Bilayer Tablet :

➢ Bi-layer execution with optional single-layer conversion kit.

➢ Cost is less as compared to all other oral dosage form.

➢ Better chemical and microbial stability over all oral dosage form.

➢ Objectionable odour and bitter taste can be inhibited by coating technique.

➢ They are unit dosage form and give the greatest potential of all oral dosage form for the greatest dose precision and the smallest content variability.

➢ Safe to swallowing with least tendency for hang-ups. [11]

Disadvantages of bilayer tablet dosage form :

➢ Few drugs withstand compression into dense compacts, due to amorphous nature, low density character. ➢ Bitter tasting drugs, drugs with an different odour or drugs that are sensitive to oxygen may need encapsulation or coating.

➢ In case of children and unconscious patients tablets are difficult to swallow.

➢ Drugs with poor wetting, slow dissolution characteristics, optimum absorption high in GIT may be critical to formulate or manufacture as a tablet that will still give full drug bioavailability. [11]

Ideal characteristics of bilayer tablets :

1. It should have simple product identity while free from defects like chips, cracks, discoloration and contamination.
2. It should have enough strength to hold mechanical shock in case of production packaging, shipping and dispensing.
3. To maintain physical characteristics over time bilayer tablets having chemical and physical stability. The bi-layer tablet must be able to release the drug in a predictable and reproducible way.
4. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.[11]

Limitations of bilayer tablet :

• One of the important tasks in bilayer formulation is absence of enough bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.

• If the compacted layers are too soft or too hard, they will not bind completely with each other which can results into compromised mechanical integrity and also the dividation of the layers.

• Other tasks during development include providing the order of layer chain, layer weight ratio, elastic mismatch of the related layers, first layer compacted force, and cross contamination between layers.

• The adjacent layers of a bilayer tablet are bind together by mechanical means, so the factors influences the stress state is very important.

• The mechanical properties of each layer and the tablet, and compression parameters along with special techniques and compression condition plays a major role for the same. Administration of sustained release bilayer tablet does not allow the prompt termination of therapy. The physician has a less flexibility on adjusting the dose regimens.[11]

TYPES OF BILAYER TABLETS :

1. Single sided tablet press.
2. Double sided tablet press.
3. Bilayer tablet press with displacement monitoring.
4. Displacement controlled tablet press .

1.Single sided press :

Now a day different types of bi-layer presses have been developed. Single-sided press with both chambers of the double feeder divided from each other is the simplest one. Each chamber is gravity or pushed fed with a various powder, thus producing the two separate layers of the tablet. When die passes under the feeder the powder of the first layer followed by second layer was loaded. Then the total tablet is compressed in one or two steps (two = pre- and main compression). Each layer-weight control on a single-sided press needs some form of measurement of the first layer and of the total tablet. The first control loop indirectly control weight and controls the fill depth of the first layer. The second loop indirectly control the total tablet weight, but adjust only second- layer fill depth. In general, compression force is necessary to monitor tablet or layer-weight. But to do so it is need to utilize a compression force to the first layer before adding the second layer-powder. To apply a compression force to the first layer before to adding the second layer, it is requirement to use two different powder feeders with a compression station in between. This is done by installing single-sided press as an additional feeder in between the pre and main compression station. Very often the precompression roller must be overcome to a much smaller size in order to make the space needed for the second feeder.

Limitations of single-sided press:

• No weight monitoring/control of the each layers

• Mixing slightly at the interface hence no distinct visual separation between the two layers

• Very short first layer-dwell time because of small compression roller, possibly leading in poor de-aeration, capping and hardness problems. This may be corrected by overcoming the turret-rotation speed but with the consequence of lower tablet output.

• Very difficult first-layer tablet sampling and sample transport to a test unit for in line quality control and weight recalibration.

2.Double sided tablet presses :

Most of the double sided tablet press, which automates production control use the compression force to monitor and control the weight of the tablet weights. The effective compression force exerted on each individual tablet with the help of the compression system at the main compression of the layer. This system helps into reject out the tolerance tablets and correct the dies fill depth when required.

The limitations of single-sided press can be overcome by a double-sided tablet press. A double-sided press offers an individual fill station, precompression and main compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the press.

• Start the feeding granules corresponds to the end of compression of the first layer. At this stage, we obtain a density distribution that is specific to a flat-faced tablet compressed such that the lower punch is stationary. In the present example, in order to get frictional effects, the friction coefficient was set, which is a relatively high value, specific to clean (un lubricated) die wall conditions.

• After compression of the first layer, the powder for the second layer is delivered into the die. The initial density of the second layer is uniform.

• At this stage, densification occurs in the second layer and the density distribution in the first layer has not yet changed.

Limitations of Double sided tablet press :

➢ Dividation of the two single layers is because of inadequate bonding between the two layers during final compression of bi-layer tablet.

➢ Correct bonding is only achieved when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression.

➢ Most of the double sided tablet presses is provided with automated controller for monitoring compression force and control tablet weight, but compression force control system is always depend on measurement of compression force at main compression but not at pre compression.

➢ At higher production rate, the risk of separation and capping increases, but it can be decreased by enough dwell time at compression stages.

3. Compression force-controlled tablet presses :

The principle of bilayer tablet press is fundamentally different from the principle of compression force. In this case the accuracy increases with reduced compression force. At higher production speed the risk of capping and separation increases, but can be reduced by sufficient dwell time a tall fourcompression stages.

During final compression of the bi-layer tablet the separation of two individual layers is occurs because of insufficient bonding in between two layers. When the first layer is compressed at a low compression force, this layer can still linked with the second layer during final compression of the tablet because of the correct bonding. Bonding is critically restricted if the first layer is compressed at a too-high compression force. The low compression force needed when compressing the first layer badly minimizes the accuracy of the weight controlling of the first layers in the case of tablet presses with “compression force measurement”. Compression force is utilized to monitor and control tablet weight in case of double-sided tablet presses with automated production control. The effective peak compression force applied on each individual tablet or layer is calculated by the control system at main compression of that layer. This minimizing sensitivity is intrinsic to an exponential relationship and therefore inherent to the compression force-controlled system. 16 The rate at which the sensitivity reduces based on the formulation or powder characteristics. This is the common reason why a compression force control system is always depends on measurement of compression force at main compression and not at pre-compression since a higher compression force is needed to get sufficient sensitivity, thus permitting a more accurate control. But; this will not occur in case of protein & peptide formulation which are more sensitive to compression force reducing pharmacological activity of protein- peptide during compression. A weight control system depends on compression force controlling is not the best solution for

first layer weight control in a bi-layer tableting process. A compression force controlled system needs a minimal compression force of several hundreds of daN. However, many bilayer formulations need a first layer compression force of less than 100 daN in order to keep the ability to bond with the second layer.

4.Displacement controlled tablet press :

The general issue, essential to the objective of compression force controlling is reduce by using a various weight controlling system depend upon 'displacement'. "Displacement measurement" as the option to "compression force measurement" has the benefit that accuracy increases with minimized compression force. Weight controlling depend upon 'displacement' also gives increased dwell-time in addition to good bonding between the two layers, with improved and accurate weight control of the first layer. A double-sided tablet press with "displacement measurement" is thus the preferred press to form bi-layer tablets.

Advantages:

• 'Displacement' weight controlling for accurate and independent weight control of the individual layers.

• Low compression force applied on the first layers to oppose capping and separation of the two single layers.

• Increased dwell time at precompression of both first and second layer to give enough hardness at maximum turret speed.

• Maximum prevention of cross-contamination between the two layers

• A clear visual separation between the two layers

• Maximized yield.[11]

VARIOUS TECHNIQUES FOR BILAYER TABLET :

There are four techniques for bilayer tablet :

1) OROS® push pull technology

2) L-OROS TM technology

3) EN SO TROL Technology

4) DUROS technology

1) OROS® push pull technology :

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer (Fig.1). The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

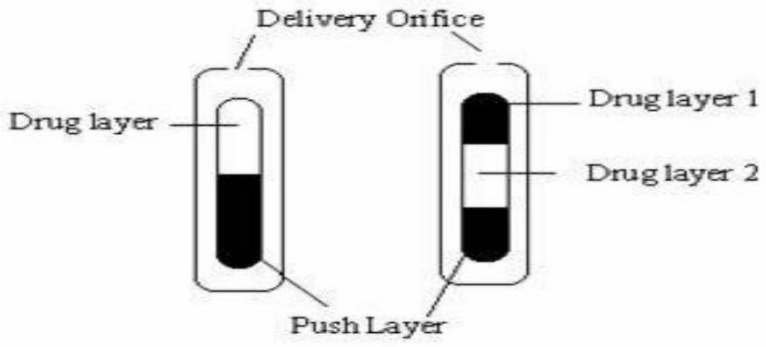


Fig. 1 : OROS Push Pull Technology

2) L-OROS TM technology :

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel Product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice (Fig.2).

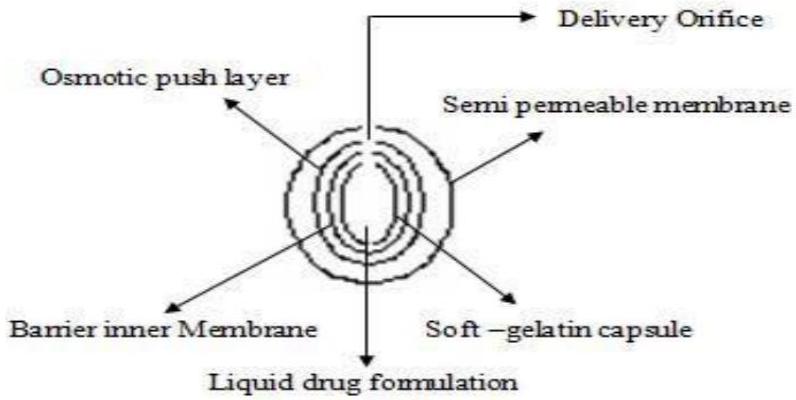


Fig. 2 : L-OROS TM Technology

3) EN SO TROL Technology :

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

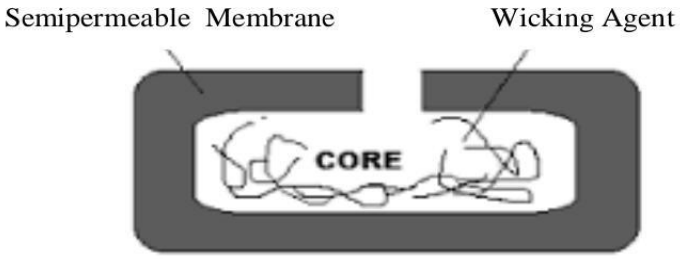


Fig . 3 : EN SO TROL Technology

4) DUROS technology :

DUROS (Alza Corporation) is based on implant technology, which gives a substitute for the delivery of a wide range of therapeutic compounds, like peptides, proteins, and other bioactive macromolecules. These implants are miniature titanium cylinders planned to give continuous osmotically driven delivery of drugs within the body for up to one year. Following implantation, DUROS implants allows continuous, exact delivery of the therapeutic compound at rates as low as 1% of a drop of water per day. The cylinder is made up from titanium because of the material's tolerability to human tissue. It is used in medical devices such as implantable defibrillators and joint replacements. The cylinder covers therapeutic molecule from degradation in the body and enables a drug to continue stable for prolonged periods of time. Latestly, Viadur (leuprolide acetate implant), which is depends on this technology, has been approved for once-yearly palliative treatment of advanced prostate cancer.[12]

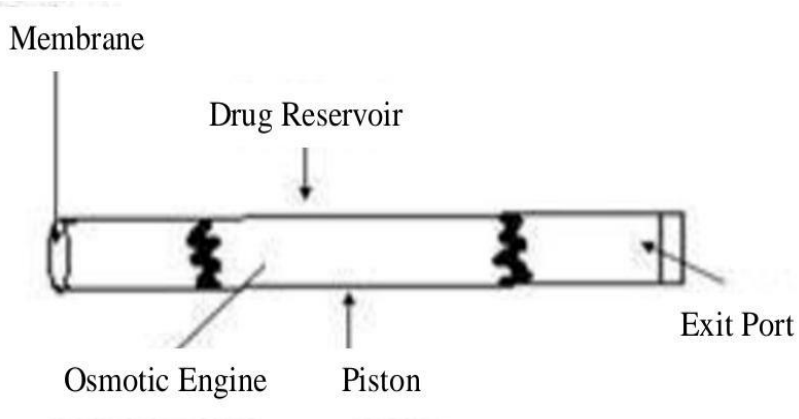


Fig. 4 : DUROS technology

Various approaches used for bilayer tablet :

a)Floating Drug Delivery System :

These are developed which having low density and thus float on gastric contents after administration. Until it remain upto disintegrates or the device absorbs fluid to the point where its density is such that it loses buoyancy and can transfer more easily from the stomach with a wave of motility responsible for gastric emptying. The bilayer tablet is developed in such a way that, one layer provides the immediate dosing of the drug which gives fast onset of action while other layer is planned as a floating layer which floats in the stomach.

Disadvantages: It may not have the controlled loss of density alternatively needed for it to exit from the stomach. In case of water soluble drugs floating tablets are not used in higher dose because it required large amounts of polymer to delay drug release. The activity of floating formulation may also be posture dependant. A patient sitting upright may ensure extended gastric residence of a buoyant dosage form, whereas a weak patient might allow ready presentation of the floating dosage form to the pylorus and thus permit fast exit of the dosage form from the stomach. Hence, floating dosage forms might be expected to only have limited applications.

b) Polymeric Bio adhesive System :

These are planned to absorb fluid following administration such that the external layer becomes a viscous, tacky material that sticks to the gastric mucosa/mucus layer. This should help gastric retention until the adhesive forces are poor. These are prepared as one layer with immediate dosing and other layer with Bio adhesive function.

Disadvantages: The success shown in animal models with such system has not been translated to human subjects because of differences in mucous amounts, uniformity between animals and humans. The system adheres only to mucous membrane. The mucous layer in humans would appear to slough off readily, possessing any dosage form with it. Therefore, Bioadhesive dosage form would not appear to give a solution for extended delivery of drug over a period of more than a few hours.

c) Swelling System :

These are planned to be adequately small on administration so as not to make ingestion of the dosage form difficult (e.g., less than upto 23 mm long and less than 11 mm wide for an oval or capsule shaped tablet whereas 10- 12mm in diameter for round tablets). On intake they quickly swell or disintegrate to a size that precludes passage via the pylorus until after drug release has progressed to a specific degree. Moderate erosion of the system or its breakdown into smaller particles enables it to leave stomach. The simple bilayer tablet consists of immediate release layer with the other layer as extended release or conventional release.[13]

Evaluation of Bilayer Tablets

1.General Appearance :

The general appearance of a tablet, its visual identity and over all elegance is essential for consumer acceptance. Includes in are tablets size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

2.Size and Shape :

The size and shape of the tablet can be dimensionally described monitored and controlled.

3.Tablet thickness :

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

4.Weight variation:

Standard procedures are followed as described in the official books.

5.Friability :

Friction and shock are the forces that most often cause the tablets to chip, chop or break. The friability testis closely related to tablet hardness and is designed to evaluate the ability of the tablet to with stand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

$$\%Friability=1-(\text{loss in weight} / \text{Initial weight})X100$$

6.Stability Study :

The bilayer tablets are packed in suitable packaging and stored under the following conditions fora period as prescribed by ICH guideline for accelerated studies. The tablets were withdrawn after a period of 15days and analyzed for physical characterizations Visual defects, Hardness, Friability and Dissolution and drug content. The data obtained is fitted into first or derequations to determine the kinetics of degradation. Accelerated stability data are plotted according Arrhenius equation to determine the shelf life at 25°C. [14]

Table 4: Commercially Marketed Bilayer Tablets.

Product Name	Chemical Name	Company Manufacturer
ALPRAXPLUS	Sertraline, Alprazolam	Torrent Pharmaceutical Ltd.
Glycomet* –GP2 Forte	Metformin hydrochloride, Glimepiride	USV Ltd.
Newcold plus	Levocetrizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramal Healthcare Ltd.
DIAMICRON*XRNEX500	Gliclazide, Metformin hydrochloride	Serdia Pharmaceutical (India) Pvt Ltd.
DIUCONTIN-K*20/250	Furosemide, Potassium chloride	T.C. Healthcare Pvt Ltd.
TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd.
PIOKIND*-M15	Pioglitazone, metaformin hydrochloride	Psychotropics India Ltd.

Bilayer Floating Tablet :

Bilayer tablet are multilayer tablets used in controlled drug delivery system. Bilayer floating tablets consisting of two layer i.e., immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface and maintain a bulk density of less than unity and thereby it remain buoyant in the stomach. The immediate release layer is comprised of gas generating system i.e., sodium bicarbonate and citric acid control release layer comprised of low density release retardant polymers like HPMC K4M, K15M, E50LV. Bilayer floating tablets can be primary option to avoid chemical in compatibility between active pharmaceutical ingredients by physical separation and to unable the development of different drug relief profile.

A novel drug delivery system overcomes the physiological problems of short gastric retention by decreasing fluctuations in blood drug concentration with subsequent reduction in undesirable toxicity and poor efficiency. Various approaches have been introduced to prolong gastric residence time, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bio-adhesive systems, high density systems, modified shape systems, etc. Bilayer floating drug delivery systems are the most promising drug delivery system, which exhibits a unique combination of floatation and bilayer, leading to prolongation in residence time in the stomach. Floatation is achieved due to bulk density being less than gastric fluids. So, the system remains buoyant in the stomach for a prolonged period, releasing the drug slowly at the desired rate and thus increasing the bioavailability of narrow absorption window drugs. This review entitles the floating drug delivery system principle and current technology used in the development. Also, it sheds light on the advantages and Total 6 disadvantages to be there disadvantages, the need for floating bilayer tablets, challenges in bi-layer tablet manufacturing, and characterization and evaluation methods for bilayer floating tablets. [15]

Table 2: Relationship between angle of repose and powder flow.

Angle of Repose	Powder Flow
<25	excellent
25-30	Good
30-40	Passable
>40	Very poor

Table 3: Limit of Weight Variation.

Weight	% Variation
Less than 80 mg	10%
80-250mg	7.50%
Above 250 mg	5%

Advantage of bilayer floating tablets : [16]

a) Lighter and compact
b) Easiest and cheapest to package and strips
c) Potentials use of single entity feed granules.
d) Traditional delivery system.
e) Maintain physical and chemical stability.
f) They offer the most flexible dosage form.
g) Masking of bitter taste and bad odour by coating.
h) Swallowing of tablets is easy.
i) Maintains constant blood level.
j) Better suited for large-scale production.
k) Less cost other than other oral dosage form
l) Chemically, mechanically and microbiologically tablets are very stable.

Disadvantage of bilayer floating tablets : [16]

a) Difficult to swallow in case of children and unconscious patients.
b) Insufficient hardness, layer separation, reduced yield.
c) Individual layer weight control.
d) Cross contamination between the layers.
e) Capping is the major problem in bilayer tablets.
f) Increased fluid levels are required in the stomach so that the system floats properly.
g) Complex and bilayer rotary press are expensive.
h) Due to low density and amorphous nature of some drugs do not form because they resist compression.
i) Sometimes encapsulation or coating is required for the drugs that are oxygen sensitive, bitter tasting and bad odour.

Limitations of bilayer floating tablets : [16]

a) Lack of sufficient bonding and adhesion at the interface between the layer result in interfacial crack and layer separation.
b) Drug, which are irritants to gastric mucosa, are not desirable.
c) The drug, which undergoes first fast metabolism, is not desirable for the preparation of these system.
d) The drugs that are unstable in the acidic environment of the stomach is not suitable.
e) Drug which has stability and solubility problem in GIT is not suitable for this system.
f) If the layer is too soft or too hard, they will not bind properly with each other which can lead to separation of the layer.
g) Bilayer tablets don't permit the termination of therapy.
h) It has less flexibility on adjusting the dose regiments.

Need of bilayer floating tablets : [16]

a) To control the delivery rate of either single or two different active pharmaceutical ingredients.
b) To modify the total surface area available API layer either by imposing with one or two inactive layers in order to achieve swellable /erodible for modified release.

c) T separate incompatible active pharmaceutical indigents from each other, to control the release of API from one layer by utilizing the functional property of other layer (such as osmotic property).

d) For the administration of fixed dose combination of drug, prolong the product life cycle, buccal/mucoadhesive delivery systems, fabricate drug delivery system such a chewing device and floating tablets for gastroretentive drug delivery systems.

Pharmacokinetic aspect of bilayer floating tablets : [17]

a) Absorption window : He candidates for GRDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at upper part of GIT.

b) Enhance bioavailability : The compound having narrow absorption window having the possibility of continuous administration of the compound at specific site.

c) Enhance first pass biotransformation : The pre-systemic metabolism of the tested compound is increased. When the drug is presented to metabolic enzyme (cytochrome p-450) in a sustained manner.

d) Improve bioavailability due to reduced p-glycoprotein activity in 16he duodenum :The drug that P-gp substrate do not undergoes oxidative metabolism GRDDS may elevate absorption compaired to immediate and CR dosage form.

e) Reduce frequency of dosing : For drugs with relatively short biological half-life. Sustained and slow input from GRDDS results flip-flop pharmacokinetic and enable reduced dosing frequency.

f) Targeted therapy for local elements in upper GIT tract : The prolonged and sustained administration of the drug from GRDDS to the stomach may produce local therapy in the stomach and small intestine.

Pharmacodynamic aspect of bilayer floating tablet : [17]

a) Reduce fluctuation of drug concentration.

b) Are associated with peak concentration can be prevented. Improved selectively in receptor activation.

c) Reduce counter activity of the body.

d)Slow input of drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

e) Minimize adverse activity of colon- The pharmacodynamics aspect provides the rationale for GRDDS formulation for beta-lactumantibiotics that are only absorbed from the small intestine and due to presence at colon it develop of microorganism is resistance.

Application of bilayer floating tablet : [17]

Bilayer tablets are suitable for the sequential release of two drugs to be given combined. It separates the two mismatching drugs. The sustained-released tablets whose one layer provides instant drug release as the initial loading dose while the second layer is containing the sustained dose. Bilayer tablets are latest technology that helps in overcoming the limitations of a single layered tablet. Bilayer tablets help in the combined delivery of two different drugs that have different release profiles. Bilayer tablets are utilized to administer fix dosage containing different APIs. They are employed to increase and modify the surface area for active pharmaceutical ingredients by erodible barriers for custom release.

A)Herbal bilayer floating tablets :

Bilayer floating tablet is the best option for herbal drug delivery. It could release drug upto 12-24 hours. It improves the therapeutic effect of drug. Some of the herbal drugs that can be delivered as bilayer floating tablets are:

i.Forskolin: It is used as anti-obesity agent reducing fat in body muscles. It may enhance fat loss without loss of muscle mass.

ii. Black myrobalan: It shows uniform anti-bacterial activity against ten clinical strains of H.pylori.

iii. Ginger root: It is used for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum and it also have chemopreventative activity in animal models.

iv. Turmeric: It prevents gastric and colon cancers in rodents**.**

v. Berberine: It shows variety of activity against bacteria, viruses, fungi, protozoans, and helminthes

B). Treatment of diseases :

i. Hypertension and angina pectoris :

Nifedipine is a calcium channel blocker of the di-hydropyridine type which is mainly used for the treatment of hypertension and angina pectoris. Nifedipine is a suitable candidate for CR administration due to its short elimination half-life of 2-hrs, its rapid and complete drug absorption over the entire gastrointestinal tract, despite its low water solubility and the relationship between drug plasma concentration and blood pressure reduction. Controlled release formulation of nifedipine would be effective in overcoming the dissolution limitation by slowly supplying the drug from the intact matrix base during its sojoum in the gastrointestinal tract and its thus expected to decrease side effect and improve patient compliance. Control release tablet for oral administration designed to deliver the drug at gastric region for treatment of hypertension. **ii.**

ii.Cardiovascular disease:

Atorvastatin immediate release and aspirin pulsatile release for the treatment of cardiovascular diseases. Four formulations were prepared for immediate release layer of atorvastatin using different concentrations of microcrystalline cellulose and talc by different compression method.

iii. Peptic ulcer:

The major target of bilayer tablet is to decrease the pain and promotes ulcer healing, prevention of complications/relapse.

C) Targeted drug delivery system :

It is the method of delivering medications to the patients in the manner that increases the concentration of medication in some part of body related to other. The aim of targeted drug delivery system is to prolong, localize, target and have protected drug interaction with the diseased tissue. It reduces the frequency of dosage taken by patient. There are different types of drug delivery route such as polymeric micelles, liposomes, lipoprotein based drug carrier, nano-particle drug carrier, dendrimers, etc. It is also used to treat cardiovascular disease and diabetes. The most important application is to treat cancerous tumours.

D) Controlled drug delivery system :

It aims at releasing the dose of therapeutic directly in the desired zone during the required period of time. It allows the maximizing the efficacy of the therapeutic and minimizing e side effects. For floating drug delivery system, the polymers used must be highly swellable in shortest time. The control release matrix tablet containing uniform mixture of drug, polymer and excipients including gas–generating agents. Nifedipine was mixed using variable amount of Carbopol p 934 and HPMC (K4M, K15M) properly in a mortar with weighed number of excipients. The well will mix powder was compressed by direct compression technique and used as controlled release layer.

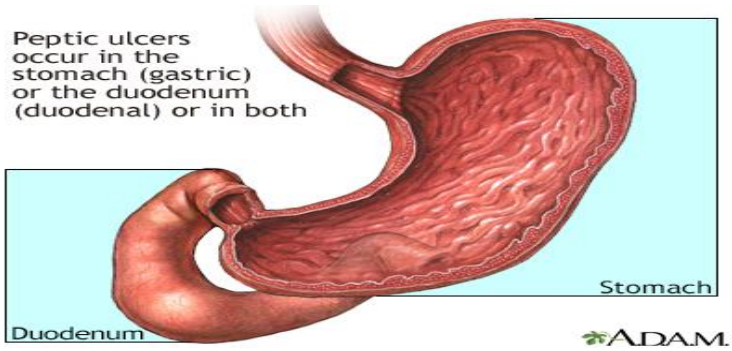
Peptic Ulcer Disease

Definition

A peptic ulcer is an open sore or raw area in the lining of the stomach or intestine.

There are two types of peptic ulcers:

- Gastric ulcer -- occurs in the stomach
- Duodenal ulcer -- occurs in the first part of the small intestine



Alternative Names :

Ulcer - peptic; Ulcer - duodenal; Ulcer - gastric; Duodenal ulcer; Gastric ulcer; Dyspepsia - ulcers; Bleeding ulcer; Gastrointestinal bleeding - peptic ulcer; Gastrointestinal hemorrhage - peptic ulcer; G.I. bleed - peptic ulcer; H. pylori - peptic ulcer; Helicobacter pylori - peptic ulcer.

There are three types of peptic ulcers:

- gastric ulcers: ulcers that develop inside the stomach.
- esophageal ulcers: ulcers that develop inside the esophagus.
- duodenal ulcers: ulcers that develop in the upper section of the small intestines, called the duodenum.

There are 4 types of gastric ulcers:

- Type 1: in the antrum, near the lesser curvature.
- Type 2: combined gastric and duodenal ulcer.
- Type 3: Prepyloric ulcer.
- Type 4: ulcer in the proximal stomach or cardia**.**

Causes

Normally, the lining of the stomach and small intestines can protect itself against strong stomach acids. But if the lining breaks down, the result may be:

- Swollen and inflamed tissue (gastritis)
- An ulcer

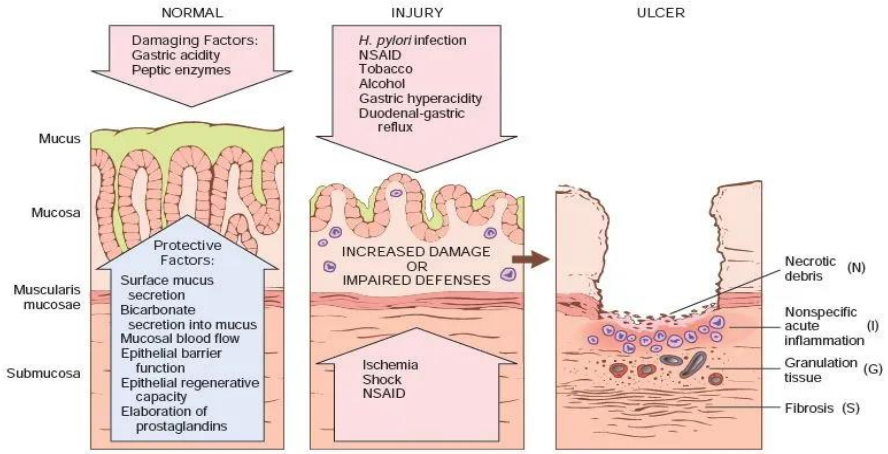
Pathophysiology

The peptic ulcer disease (PUD) mechanism results from an imbalance between gastric mucosal protective and destructive factors. Risk factors predisposing to the development of PUD:

- *H. pyl*ori infection
- NSAID use
- First-degree relative with PUD
- Emigrant from a developed nation
- African American/Hispanic ethnicity

With peptic ulcers, there is usually a defect in the mucosa that extends to the muscularis mucosa. Once the protective superficial mucosal layer is damaged, the inner layers are susceptible to acidity. Further, the ability of the mucosal cells to secrete bicarbonate is compromised.

H. pylori is known to colonize the gastric mucosa and causes inflammation. The H. pylori also impairs the secretion of bicarbonate, promoting the development of acidity and gastric metaplasia.



Etio pathogenesis

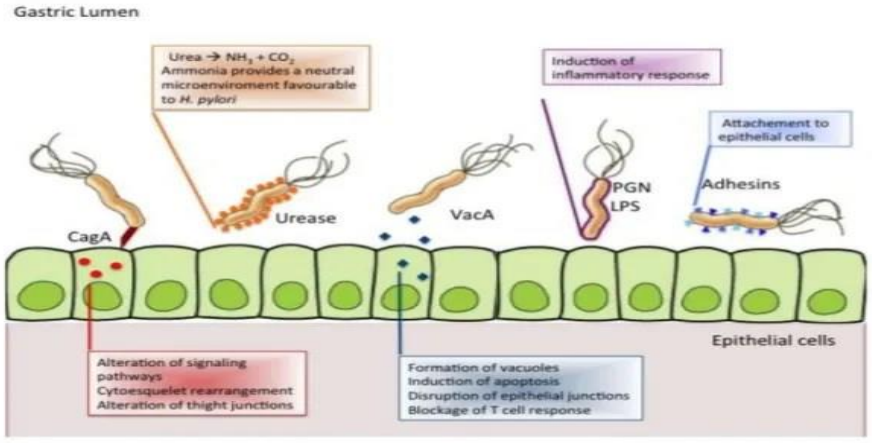
Peptic ulcers develop because of –

- Fall in mucosal defenses
- Decreased mucosal blood flow
- Delayed gastric emptying
- Impaired epithelial restitution
- Impaired prostaglandin synthesis

ETIOLOGICAL FACTORS

- **H.PYLORI INFECTION** –Host factors as well as variation among H.pylori strains determine the clinical outcomes.
- Helicobacter Pylori is Gram negative, nonsporing curvilinear bacilli, measuring 5 x 0.5 µm

- H.pylori genome encodes 1500 proteins
- H.pylori causes gastritis by 2 ways :
- Direct injury of epithelial cells
- Stimulating production of pro-inflammatory cytokines (IL – 1β and TNF)
- **Pathogenesis of H.pylori**
- H.pylori moves in the viscous mucin layer via flagella
- It has Urease which produces ammonia from endogenous urea and buffers gastric acid in the immediate vicinity of organism
- Expresses of Bacterial adhesins that enhances the bacterial adherence to foveolar cells
- Expression of Bacterial toxins
- Cag A (Cytotoxin associated gene A protein) – Cytotoxin which alters signaling pathway, alters the cytoskeletal rearrangement and alters the tight junctions between the cells
- Vac A (Vacuolating cytotoxin gene A protein) – It causes formation of vacoules in the cells, induces apoptosis, causes disruption of epithelial junctions and blocks the T cells response
- H.pylori infection often presents as antral gastritis with normal or increased acid production
- In severe cases presents as pan gastritis
- H.pylori infection along with host factors like increased expression of proinflammatory cytokines like TNF, IL-1β or decreased expression of anti-inflammatory cytokines like IL-10 leads to pangastritis, atrophy, and gastric cancer



- ZOLLINGER ELLISON SYNDROME – uncontrolled release of gastrin by a tumor and the resulting massive acid production
- CHRONIC NSAID USE-
- suppress prostaglandin synthesis necessary for mucosal protection
- Toxic injury to the epithelium and endothelium
- DRUGS LIKE COCAINE – reduces mucosal blood flow
- CIGARETTE SMOKING, which impairs mucosal blood flow and healing
- PSYCHOLOGICAL STRESS may increase gastric acid production.
- GENETIC FACTORS – people with blood group O are more prone for the development of peptic ulcer
- VIRAL INFECTIONS like CMV and herpes simplex virus

PATHOGENESIS :

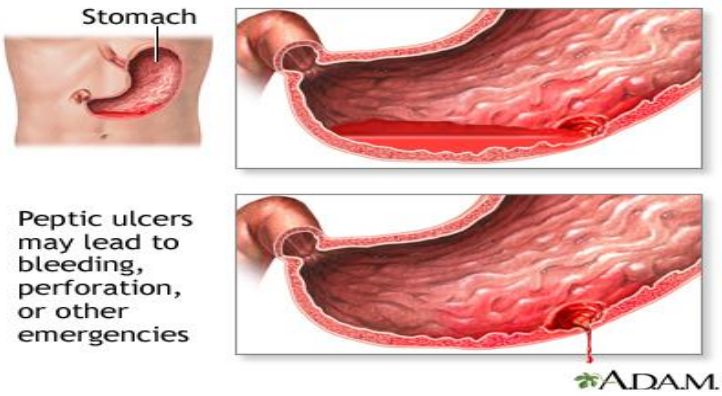
Different pathogenetic mechanism involved in gastric and duodenal ulcers

- Duodenal ulcers- Mechanism for the development of duodenal ulcers
- Mucosal digestion from hyperacidity and damage to mucosal barrier. This is due to
- Hypersecretion of gastric acid into the stomach at night under the influence of vagal stimulation

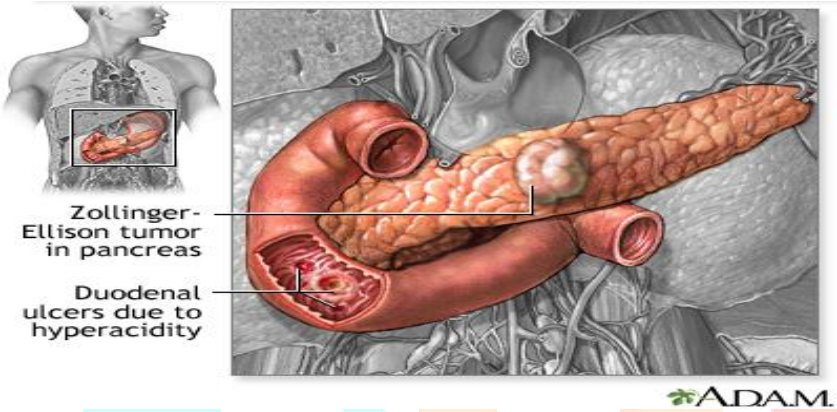
- Rapid emptying of stomach so that food which normally neutralizes the gastric acid passes into the small intestine so that aggressive acid acts on duodenal mucosa
- H.pylori gastritis –
- Gastric mucosal defense is broken down by bacterial urease, protease, catalase and phospholipase.
- Host factors – H.pylori infected mucosal epithelium releases proinflammatory cytokines such as IL-1, IL-6, Il-8 and tumor necrosis factor –alpha
- Bacterial factors – epithelial injury induced by Cag A protein and Vac A which induces secretion of cytokines
- Gastric ulcer
- Mainly due to impaired gastric mucosal defenses against acid –pepsin secretions
- Mucosal defense mechanism is
- Mucous layer with bicarbonate
- Surface epithelium
- Mucin has acid resistant property and this is enhanced by secretion of sodium and bicarbonate by the epithelial cells into mucin which neutralizes the HCl.
- Surface epithelium forms second line of defense. An adequate blood supply to the mucosa is important for these functions
- An ulcer results due to failure of this defense mechanism.
- H.Pylori colonization in gastric mucosa
- Trauma due to spicy food or alcohol
- Smoking impairs mucosal blood flow and impairs healing
- Hyperacidity – due to increased serum gastrin levels in response to ingested food in atonic stomach
- Incompetence of pyloric sphincter leads to bile reflux which damages the mucosal barrier. Cigarette smoking reduces the resting tone of the sphincter

Stomach Ulcer :

- The stomach is the organ of the digestive system in which food travels from the esophagus and is further broken down before its nutrients are absorbed in the small intestine. It produces acid and various enzymes that break down food into simple substances. The inside wall of the stomach is protected from the acid and enzymes by a mucous lining. Ulcers are caused when there is an imbalance between the digestive juices produced by the stomach and the various factors that protect the lining of the stomach. Symptoms of ulcers may include bleeding. On rare occasions, an ulcer may completely erode the stomach wall. A major cause of stomach ulcers is the bacteria called Helicobacter pylori. Treatment regimens for ulcers caused this bacterium usually include medications to suppress the stomach acid as well as antibiotics to eradicate the infection.
- Most ulcers occur in the first, inner surface, layer of the inner lining. A hole in the stomach or duodenum is called a perforation. This is a medical emergency.



- The most common cause of ulcers is infection of the stomach by bacteria called Helicobacter pylori (H pylori). Most people with peptic ulcers have these bacteria living in their digestive tract. Yet, many people who have these bacteria in their stomach do not develop an ulcer.
- The following factors raise your risk for peptic ulcers:
- Drinking too much alcohol
- Regular use of aspirin, ibuprofen, naproxen, or other nonsteroidal anti-inflammatory drugs (NSAIDs)
- Smoking cigarettes or chewing tobacco
- Being very ill, such as being on a breathing machine
- Radiation treatments
- Stress
- A rare condition, called Zollinger-Ellison syndrome, causes the stomach to produce too much acid, leading to stomach and duodenal ulcers.



Symptoms

Small ulcers may not cause any symptoms and may heal without treatment. Some ulcers can cause serious bleeding.

Abdominal pain (often in the upper mid-abdomen) is a common symptom. The pain can differ from person to person. Some people have no pain.

Pain occurs:

- In the upper abdomen
- At night and wakes you up
- When you feel an empty stomach, often 1 to 3 hours after a meal

Other symptoms include:

- Feeling of fullness and problems drinking as much fluid as usual
- Nausea
- Vomiting
- Bloody or dark, tarry stools
- Chest pain
- Fatigue
- Vomiting, possibly bloody
- Weight loss
- Ongoing heartburn

Factors affecting gastric residence time of the floating drug delivery system :

Formulation factors :

Size of tablets

Floating retention phenomenon of dosage forms in the stomach basically depends on the size of tablets. Small tablets are expelled rapidly from the stomach compared to large ones are emptied during the digestive phase.

Density of tablets

Density also considered as contributing factor affecting the gastric residence time of dosage form. A buoyant dosage with a density less than that of the gastric fluids would float as it is long enough from the pyloric

sphincter, thus having more retention in the stomach for a longer period. Density tablets about 1.0 g/ml (usually considered as less dense than that of gastric contents) have been reported more effective. However, the floating force kinetics has shown that the bulk density of a dosage form would not be the crucial parameter affecting its buoyancy capabilities.

Shape of tablets

The shape of the dosage form is also considered as one of the affecting factors as it interferes with gastric residence time. Six different types of shapes viz. ring tetrahedron, cloverleaf, string, pellet, and disk) are screened in vivo for their gastric retention potential; during this study, the tetrahedron shape (each leg 2 cm long) rings (3.6 cm in diameter) passed nearly 100% retention at 24 h.

Viscosity of polymers

Drug release and floating characters of FDDS are majorly affected by the viscosity of different grade of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) are found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in enhancing the floating properties of the dosage form. Moreover, a decrease in the release rate was also found with an increase in polymer viscosity.

Idiosyncratic factors :

Gender

A study shows women have slower gastric emptying time in comparison with men. Mean ambulatory gastric retention time in men (3.4±0.4 h) is lower in comparison with their age and race with female counterparts (4.6±1.2 h), regardless of the weight, height and body surface.

Age

Lower gastric emptying time is also observed with high frequent in elderly than do in younger. Intra and inter-person variations are also existing in gastric and intestinal transit time. Elderly people, especially those over 70 y have a significantly longer gastric retention time.

Posture

Upright position

An upright position prolongs floating forms against postprandial emptying since the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show longer and reproducible gastric retention time while the conventional dosage forms tend to sink at the lower part of the distal stomach from where they are expelled through the pylorus by peristaltic movements.

Supine position

This position does not offer any reliable protection against early and erratic emptying. In supine subjects, large dosage forms (both conventional and floating) may experience longer retention. The gastric retention of floating forms appears to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to a significant reduction in gastric retention time compared with upright subjects.

Concomitant intake of drugs

Different drugs with a concomitant intake like prokinetic agents (e.g., metoclopramide and cisapride), anticholinergic (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of the floating drug delivery system. The co-administration of GI motility decreasing drugs can increase gastric emptying time and vice versa.

Feeding regimen

Gastric residence time shows enhancement in the presence of food, leading to increased drug dissolution rate of the dosage form at the favorable site of absorption. A gastric retention time of about 4 to 10 h has been reported after a diet of fats and proteins.

The mechanism associated with FDDS

FDDS is one of the presidential approaches in achieving gastric retention with sufficient drug bioavailability. This system is selective for the drugs with an absorption window in the stomach or in the upper small intestine. This has a less density then gastric fluids and hence remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period, and the drug is released slowly as a desired rate from the system. After

the release of the drug, the residual system is expelled from the stomach. This results in an increased gastric retention time and better control on the fluctuation in plasma drug concentration.

Pharmacokinetic and pharmacodynamic aspects of FDDS :

Enhanced bioavailability

FDDS has studied with excellence increase in bioavailability of certain drugs with low therapeutic window solely due to poor GI absorption due to various factors contributing to lower bioavailability. The drugs those considered with narrow absorption window, FDDS shown the possibility of with enhanced bioavailability of the compound to the specific site needed. The bioavailability of control release (CR) floating systems of Riboflavin and Levodopa are significantly enhanced in comparison to the administration of the conventional formulation. On the other hand, CR polymeric formulations of certain bisphosphonates, including alendronate, are absorbed directly from the stomach. However, the magnitude of this pathway remains modest even in the case where the prolonged gastric retention of the bisphosphonate in rats is produced by experimental/surgical means. It may be concluded that several different processes, related to absorption and transit of the drug in the gastrointestinal tract, act concomitantly and influence the magnitude of drug absorption.

Enhanced first-pass biotransformation

In a similar fashion to increased efficacy of active transporters exhibiting limited capacity activity, the pre-systemic metabolism of the tested compound has considerably increased cause of FDDS, if the drug is presented to the metabolic enzymes (cytochrome P450, in particular, CYP3A4) in a sustained manner, rather than by a bolus input.

Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum

In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gp mRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as Digoxin, floating systems may elevate absorption compared to the immediate and control release (CR) dosage forms.

Reduced frequency of dosing

The different studies reveal that the drugs those contributing relatively short biological half-life, slow input from sustained release and control release floating system flip-flop pharmacokinetics assured with reduced dosing frequency were observed. This feature is associated with improved patient compliance, and thereby improves therapy.

Targeted therapy for local ailments in the upper GIT

The prolonged and sustained administration of the drug from the floating systems to the stomach may be advantageous for local therapy in the stomach and the small intestine.

Pharmacodynamic aspects of FDDS :

Reduced fluctuations of drug concentration

Floating system of drug administration produces constant blood drug concentrations within a narrower range in comparison to the immediate release dosage forms on continuous input of the drug. Thus, fluctuations in drug effects are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is especially advantageous for drugs with a narrow therapeutic index.

Improved selectivity in receptor activation

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

Reduced counter-activity of the body

In many cases, the pharmacological response, which intervenes with the natural physiologic processes, provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body as incase of FDDS is shown to minimize the counter activity leading to higher drug efficiency.

Minimized adverse activity at the colon

Retention of the drug in the FDDS specifically in case of gastro retentive form at the stomach minimizes the amount of drug that reaches down the colon. Thus, undesirable activities of the drug in colon may be prevented.

This pharmacodynamic aspect provides the rationale for floating formulation for beta-lactam antibiotics that are absorbed only from the small intestine and presence in the colon leads to the development of microorganisms.

Famotidine

Drug Name : Famotidine

Famotidine is a histamine H_2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease. In the management of benign gastric and duodenal ulceration the dose is 40 mg daily by oral route at bedtime, for 4 to 8 weeks. In gastroesophageal reflux disease the recommended dose is 20 mg by oral route twice daily for 6 to 12 weeks. Famotidine is incompletely absorbed from GI tract, the low bioavailability (40-45%) and short biological half-life (2.5-3.5 h) of famotidine following oral administration favors development of a sustained release formulation.

Famotidine is a competitive histamine-2 (H_2) receptor antagonist that works to inhibit gastric acid secretion. It is commonly used in gastrointestinal conditions related to acid secretion, such as gastric ulcers and gastroesophageal reflux disease (GERD), in adults and children. Compared to other H_2 receptor antagonists, famotidine displays high selectivity towards this receptor; in a study consisting of healthy volunteers and patients with acid hypersecretory disease, famotidine was about 20 to 50 times more potent at inhibiting gastric acid secretion than cimetidine and eight times more potent than ranitidine on a weight basis. Famotidine is used in various over-the-counter and off-label uses. While oral formulations of famotidine are more commonly used, the intravenous solution of the drug is available for use in hospital settings.

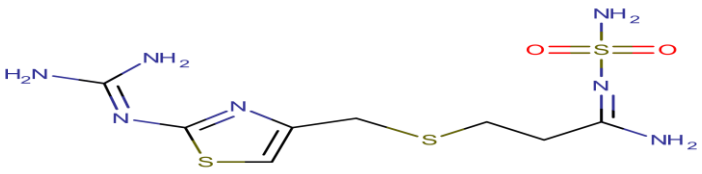
Famotidine belongs to the group of medicines known as histamine H2-receptor antagonists or H2-blockers. It works by decreasing the amount of acid produced by the stomach.

This medicine is available with your doctor's prescription and also without a prescription. For the prescription form, there is more medicine in each tablet. Your doctor will have special instructions on the proper use and dose for your medical problem.

This product is available in the following dosage forms:

- Tablet
- Powder for Suspension

Structure :



Generic Name :

Famotidine

Brand Names :

Duexis, Duo Fusion, Fluxid , Good Sense Acid Reducer, Pepcid, Pepcid Complete, Zantac Reformulated Aug 2022

Chemical Formula :

$C_8H_{15}N_7O_2S_3$

IUPAC Name :

3-[({2-[(diaminomethylidene)amino]-1,3-thiazol-4-yl}methyl)sulfanyl]-*N*-sulfamoylpropanimidamide

Molecular Weight :

337.5 g/mol

Density :

Famotidine Powder Density : 1.838 g/cm

Melting point :

163.5°C

Boiling Point :

662.383 °C at 760 mmHg

Colour :

White to pale yellow crystals

Taste :

Bitter taste

Odor :

Odorless

State :

Solid crystals

Solubility :

1000mg/L (at 20 °C)

Freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Solubility in water :

0.1% (w/v) at 293 K

Route Of Administration :

20 mg of famotidine either orally and twice daily or via IV route every 12 hours.

Pharmacodynamics :

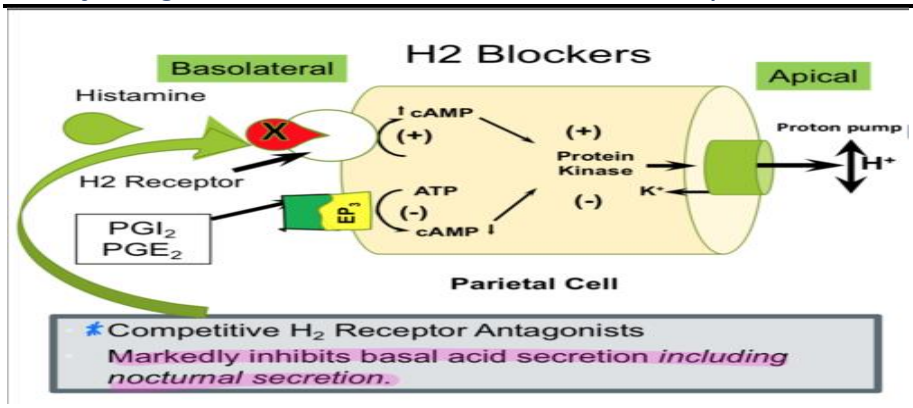
Famotidine decreases the production of gastric acid, suppresses acid concentration and pepsin content, and decreases the volume of gastric secretion. Famotidine inhibits both basal and nocturnal gastric acid secretion, as well as acid secretion stimulated by food, caffeine, insulin, and pentagastrin.

Famotidine has a dose-dependent therapeutic action, with the highest dose having the most extended duration of action and the highest inhibitory effect on gastric acid secretion. Following oral administration, the onset of action is within one hour, and the peak effect is reached within 1-3 hours. The duration of effect is about 10-12 hours.

Mechanism of action :

Histamine acts as a local hormone that stimulates the acid output by parietal cells via a paracrine mechanism. Neuroendocrine cells called enterochromaffin-like (ECL) cells lie close to the parietal cells and regulate the basal secretion of histamine. Histamine release is also promoted from stimulation by acetylcholine and gastrin, a peptide hormone. Gastrin (G) cells release gastrin, which works on CCK_2 receptors on ECL cells. This action promotes the release of histamine from ECL cells. Upon release, histamine acts on H_2 receptors expressed on the basolateral membrane of parietal cells, leading to increased intracellular cAMP levels and activated proton pumps on parietal cells. Proton pump releases more protons into the stomach, thereby increasing the secretion of acid. In conditions that are associated with acid hypersecretion such as ulcers, there is a loss of regulation of acid secretion. Famotidine works on H_2 receptors and blocks the actions of histamine.

- Work by reversibly inhibiting H2 receptors
- Receptors present on gastric parietal cells
- Lowers gastric acid secretion



Absorption :

Following oral administration, the absorption of famotidine is dose-dependent and incomplete. The oral bioavailability ranges from 40-50%, and the Cmax is reached in 1-4 hours post-dosing. While the bioavailability can be slightly increased with the intake of food and decreased by antacids, there is no clinical significance.

Volume of distribution :

The steady-state volume of distribution ranges from 1.0 to 1.3 L/kg. Famotidine is found in breast milk; however, it is found in breast milk at the lowest concentrations compared to other H_2 receptor antagonists.

Protein binding :

The protein binding of famotidine is about 15 to 22%.

Metabolism :

Famotidine undergoes minimal first-pass metabolism. About 25-30% of the drug is eliminated through hepatic metabolism. The only metabolite identified in humans is the S-oxide.

Route of elimination :

About 65-70% of the total administered dose of famotidine undergoes renal elimination, and 30-35% of the dose is cleared by metabolism. Following intravenous administration, about 70% of the drug is eliminated in the urine as an unchanged drug.

Half-life :

The elimination half-life is about 2 to 4 hours. The half-life is expected to increase nonlinearly in patients with decreased renal function.

Clearance :

Renal clearance is 250-450 mL/min, indicating some tubular excretion. Because the renal clearance rate exceeds the glomerular filtration rate, famotidine is thought to be mainly eliminated via both glomerular filtration and renal tubular secretion.

Adverse Effects :

The more common adult side effects for this drug are slightly different from the more common side effects for children.

- Adult side effects can include:
  - headache
  - dizziness
  - constipation
  - diarrhea
- Children under one year of age may also experience:
  - agitation, unusual restlessness, or crying for no clear reason.

Serious side effects :

- Heart rate and rhythm problems. Symptoms can include:
  - dizziness

- fainting
- shortness of breath
- irregular heart rate and rhythm

- Severe muscle problems. Symptoms can include:
  - unusual muscle pain that you cannot explain
  - weakness
  - fever
- Neurological problems. Symptoms can include:
  - agitation
  - anxiety
  - depression
  - trouble sleeping
  - seizures
  - sexual problems, such as decreased sex drive
- Liver problems. Symptoms can include:
  - unexplained or unusual weakness
  - decrease in appetite
  - pain in your abdomen (stomach area)
  - change in the color of your urine
  - yellowing of your skin or the whites of your eyes
- Skin problems. Symptoms can include:
  - blisters
  - rash
  - mouth sores or ulcers

Toxicity :

The oral LD_{50} is 4049 mg/kg in rats and 4686 mg/kg in mice. The subcutaneous LD_{50} is 800 mg/kg in rats and mice. The intraperitoneal LD_{50} is 800 mg/kg in rats and 778 mg/kg in mice. The intravenous LD_{50} is 204 mg/kg in rats and 254 mg/kg in mice. The lowest published toxic dose (TDLo) in man following oral administration is 4 mg/kg/7D.

Symptoms of overdose resemble the adverse events seen with the use of recommended doses, and they should be responded with supportive and symptomatic treatment. Any unabsorbed drug should be removed from the gastrointestinal tract, and the patient should be monitored accordingly. The use of hemodialysis to eliminate the drug from the systemic circulation is effective, but the experience of using hemodialysis in response to famotidine overdose is limited in clinical settings.

Medical uses :

- Heartburn, acid indigestion, and sour stomach
- Treatment for gastric and duodenal ulcers
- Treatment for pathologic gastrointestinal hypersecretory conditions such as Zollinger–Ellison syndrome and multiple endocrine adenomas
- Treatment for gastroesophageal reflux disease (GERD)
- Treatment for esophagitis
- Part of a multidrug regimen for Helicobacter pylori eradication, although omeprazole may be somewhat more effective.
- Prevention of NSAID-induced peptic ulcers.
- Given to surgery patients before operations to reduce the risk of aspiration pneumonitis.

Contraindication :

Famotidine is contraindicated for patients with hypersensitivity to famotidine or any of its formulation components. Due to observed cross-sensitivity among H2RAs, famotidine should not be prescribed to patients with a history of hypersensitivity to cimetidine. Furthermore, OTC tablets should not be used by patients experiencing difficulties or pain while swallowing food, exhibiting vomiting with blood, or noticing the presence of bloody or black stools. The OTC famotidine tablets should also not be administered to patients who are allergic to or are currently taking other acid reducers, as well as those with renal impairment.

Indication :

Famotidine is indicated in pediatric and adult patients (with the bodyweight of 40 kg and above) for the management of active duodenal ulcer (DU), active gastric ulcer, symptomatic non-erosive gastroesophageal reflux disease (GERD), and erosive esophagitis due to GERD, diagnosed by biopsy.

It is also indicated in adult patients for the treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine neoplasias) and reduction of the risk of DU recurrence.

The intravenous formulation of famotidine is available for some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.

Over-the-counter famotidine is used for the management and prevention of heartburn caused by gastroesophageal reflux in children and adults. Off-label uses of famotidine include the reduction of NSAIDs-associated gastrointestinal effects, treatment of refractory urticarial, prevention of stress ulcer in critically-ill patients, and symptomatic relief of gastritis.

Clindamycin

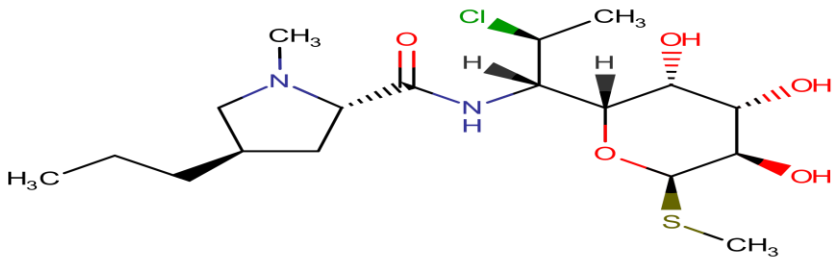
Drug Name : Clindamycin

Clindamycin is a lincosamide antibiotic used to treat serious infections caused by susceptible anaerobic, streptococcal, staphylococcal, and pneumococcal bacteria.

Clindamycin is a semi-synthetic lincosamide antibiotic used in the treatment of a variety of serious infections due to susceptible microorganisms as well as topically for acne vulgaris. It has a relatively narrow spectrum of activity that includes anaerobic bacteria as well as gram-positive cocci and bacilli and gram-negative bacilli. Interestingly, clindamycin appears to carry some activity against protozoans, and has been used off-label in the treatment of toxoplasmosis, malaria, and babesiosis.

Clindamycin is derived from, and has largely replaced, lincomycin, a naturally occurring lincosamide and the eponymous member of this antibiotic class, due to its improved properties over the parent compound. The name lincomycin is derived from Lincoln, Nebraska, where it was first isolated from Streptomyces lincolnensis found in a soil sample.

Structure :



Brand Names :

Acanya, Benzaclin, Biacna , Cabtreo, Cleocin, Cleocin-T, Clindacin, Clindagel, Clindesse, Clindoxyl, Dalacin, Dalacin C, Duac, Evoclin, Neuac, Onexton, Veltin, Xaciato, Ziana

Generic Name :

Clindamycin

Chemical Formula :

$C_{18}H_{33}ClN_2O_5S$

IUPAC Name :

(2S,4R)-N-[(1S,2S)-2-chloro-1-[(2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-methylsulfanyloxan-2-yl]propyl]-1-methyl-4-propylpyrrolidine-2-carboxamide

Molecular Weight :

425.0 g/mol

Density :

The loose bulk density and tapped bulk density for all the formulations varied from 0.35gm/cm3 to 0.43gm/cm3 and 0.42gm/cm3 to 0.44gm/cm3 respectively.

Melting point :

141-143 ^{0}C

Colour :

Yellow.

Taste :

Bitter taste

Odor:

odorless or with a faint mercaptan-like odor .

State :

white or practically white crystalline powder and amorphous solid .

Solubility:

Water soluble

Solubility in water :

Solubility is between 200 and 300 mg/ml

Route Of Administration :

Clindamycin is administered by intravenous (IV) intermittent infusion over at least 10 to 60 minutes at a maximum rate of 30 mg/min.

The final concentration of the IV solution should not exceed 18 mg/mL.

Pharmacodynamics :

Clindamycin exerts its bacteriostatic effect via inhibition of microbial protein synthesis. Clindamycin has a relatively short T_{max} and half-life necessitating administration every six hours to ensure adequate antibiotic concentrations.

Clostridium difficile associated diarrhea (CDAD) has been observed in patients using clindamycin, ranging in severity from mild diarrhea to fatal colitis and occasionally occurring over two months following cessation of antibiotic therapy. Overgrowth of *C.* difficile resulting from antibiotic use, along with its production of A and B toxins, contributes to morbidity and mortality in these patients. Because of the associated risks, clindamycin should be reserved for serious infections for which the use of less toxic antimicrobial agents are inappropriate.

Clindamycin is active against a number of gram-positive aerobic bacteria, as well as both gram-positive and gram-negative anaerobes. Resistance to clindamycin may develop, and is generally the result of base modification within the 23S ribosomal RNA. Cross-resistance between clindamycin and lincomycin is complete, and may also occur between clindamycin and macrolide antibiotics (e.g. erythromycin) due to similarities in their binding sites.

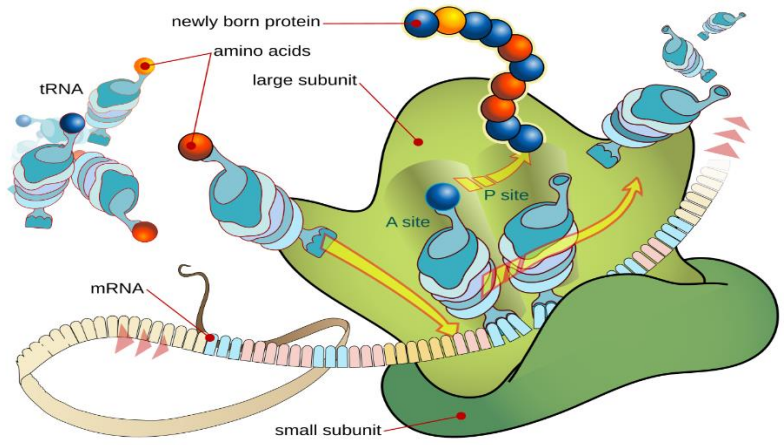
As antimicrobial susceptibility patterns are geographically distinct, local antibiograms should be consulted to ensure adequate coverage of relevant pathogens prior to use.

Mechanism of action :

Clindamycin inhibits bacterial protein synthesis by binding to 23S RNA of the 50S subunit of the bacterial ribosome. It impedes both the assembly of the ribosome and the translation process. The molecular mechanism through which this occurs is thought to be due to clindamycin's three-dimensional structure, which closely resembles the 3'-ends of L-Pro-Met-tRNA and deacylated-tRNA during the peptide elongation cycle - in acting as a structural analog of these tRNA molecules, clindamycin impairs peptide chain initiation and may stimulate dissociation of peptidyl-tRNA from bacterial ribosomes.

The mechanism through which topical clindamycin treats acne vulgaris is unclear, but may be related to its activity against Propionibacterium acnes, a bacteria that has been associated with acne.

- Clindamycin has a primarily bacteriostatic effect.
- Inhibits protein synthesis by binding to the 50s.



Absorption :

Oral bioavailability is nearly complete, at approximately 90%, and peak serum concentrations (C_{max}) of, on average, 2.50 µg/mL are reached at 0.75 hours (T_{max}). The AUC following an orally administered dose of 300mg was found to be approximately 11 µg•hr/mL. Systemic exposure from the administration of vaginal suppository formulations is 40-fold to 50-fold lower than that observed following parenteral administration and the C_{max} observed following administration of vaginal cream formulations was 0.1% of that observed following parenteral administration.

Volume of distribution :

Clindamycin is widely distributed in the body, including into bone, but does not distribute into cerebrospinal fluid. The volume of distribution has been variably estimated between 43-74 L.

Protein binding :

Clindamycin protein binding is concentration-dependent and ranges from 60-94%. It is bound primarily to alpha-1-acid glycoprotein in the serum.

Metabolism :

Clindamycin undergoes hepatic metabolism mediated primarily by CYP3A4 and, to a lesser extent, CYP3A5. Two inactive metabolites have been identified - an oxidative metabolite, clindamycin sulfoxide, and an N-demethylated metabolite, N-desmethylclindamycin.

Route of elimination :

Approximately 10% of clindamycin bioactivity is excreted in the urine and 3.6% in the feces, with the remainder excreted as inactive metabolites.

Half-life :

The elimination half-life of clindamycin is about 3 hours in adults and 2.5 hours in children. Half-life is increased to approximately 4 hours in the elderly.

Clearance:

The plasma clearance of clindamycin is estimated to be 12.3-17.4 L/h, and is reduced in patients with cirrhosis and altered in those with anemia.

Adverse Effects :

- nausea
- vomiting
- unpleasant or metallic taste in the mouth
- joint pain
- pain when swallowing
- heartburn
- white patches in the mouth

Toxicity:

The oral LD_{50} in mice and rats is 2540 mg/kg and 2190 mg/kg, respectively.

While no cases of overdose have been reported, symptoms are expected to be consistent with the adverse effect profile of clindamycin and may therefore include abdominal pain, nausea, vomiting, and diarrhea. During clinical trials, one 3-year-old child was given a dose of 100 mg/kg daily for 5 days and showed only mild abdominal pain and diarrhea. Activated charcoal may be of value to remove unabsorbed drug, but hemodialysis and peritoneal dialysis are ineffective. General supportive measures are recommended in cases of clindamycin overdose.

Medical Use :

Clindamycin may be used to treat a wide range of infections, although it should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria to reduce the development of drug-resistant bacteria and to maintain its effectiveness.

Infections clindamycin treats in adults and children include serious:

- Infections caused by susceptible anaerobic bacteria
- Infections due to susceptible isolates of streptococci, pneumococci, and staphylococci, if a less toxic alternative (such as erythromycin) is not suitable
- Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by susceptible isolates of anaerobes, Streptococcus pneumoniae, other streptococci (except Enterococcus faecalis), and Staphylococcus aureus in adults and children
- Skin and skin structure infections caused by susceptible isolates of Streptococcus pyogenes, Staphylococcus aureus, and anaerobes in adults and children
  - Topical clindamycin 1% may be used to help treat and control severe acne.
- Gynecological infections including endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection caused by susceptible anaerobes in adults and children

Contraindications :

Clindamycin is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

Indication :

In oral and parenteral formulations, clindamycin is indicated for the treatment of serious infections caused by susceptible anaerobic bacteria, as well as susceptible staphylococci, streptococci, and pneumococci. Used topically, it is indicated for the treatment of acne vulgaris and is available in combination with benzoyl peroxide or tretinoin for this purpose, or as a triple combination therapy with benzoyl peroxide and adapalene. Clindamycin is also indicated as a vaginal cream, suppository, or gel for the treatment of bacterial vaginosis in non-pregnant females.

Clindamycin is used for antimicrobial prophylaxis against Viridans group streptococcal infections in susceptible patients undergoing oral, dental, or upper respiratory surgery, and may be used for prophylaxis against bacterial endocarditis in penicillin-allergic patients at high risk of these infections.

METHODOLOGY

Preformulation studies

Preformulation testing is the first step in rational development of dosage forms of a drug substance. Preformulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, preformulation studies were performed for the obtained sample of drug for identification and compatibility studies.

Identification-

A. Organoleptic properties:

Colour : A colour of Famotidine are White to pale yellow crystals and a colour of Clindamycin are Yellow.

Taste : Famotidine : Bitter taste

Clindamycin : Bitter taste

Odour: Famotidine : Odorless

Clindamycin : odorless or with a faint mercaptan-like odor .

B. Flow properties :

1) Angle of repose :

Angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\tan \theta = h / r$$

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

where, θ = angle of repose,

h = height of heap,

r = radius of base of heap circle.

A funnel was fixed at a height approximately 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the tip of powder cone so formed just touched the tip of funnel stem. Angle of repose was then determined by measuring the height of the cone of powder and radius of the circular base of powder heap.

Table No.1: Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	> 66

2)Bulk Density :

Bulk density of was determined by pouring gently known quantity of powder sample through a glass funnel into graduated measuring cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated using following formula.

$$\text{Bulk Density} = \frac{\text{Weight of sample in gm.}}{\text{Bulk volume}} \quad \text{gm/ml.}$$

3)Tapped Density :

The powder sample was poured gently through glass funnel into graduated measuring cylinder. Initial volume of powder was noted and the sample subjected to tapping (500, 750 or 1250 tappings) until no further reduction in volume was noted or the percentage of difference in volume was not more than 2 %. Volume occupied by the samples after tapping was recorded and tapped density was calculated using following formula.

$$\text{Tapped density} = \frac{\text{Weight of sample in gm}}{\text{Volume after tapping}} \quad \text{gm/ml}$$

Table No.2- : Scale of Flowability

Compressibility index (%)	Flow character	Hausner ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
> 38	Very, very poor	> 1.60

4)Compressibility index and Hausner ratio :

In recent years compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials

because all of these can influence the observed compressibility index. The compressibility index and Hausner ratio are determined by measuring both bulk density and the tapped density of a powder.

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table No.3 : Compressibility Index

Compressibility Index	Flow Character	Hausner Ratio
1-10	Excellent	1-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21- 25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table No.4 : Hausner ratio

Hausner ratio	Property
0 - 1.2	Free flowing
1.2 - 1.6	Cohesive Powder

Loss On Drying (LOD) – Determined 1 gm by drying in an oven at 100^0c to $105^0$for 3 hours. Mixed & accurately weighed the substances to be tasted .Tarred a glass stoppered, shallow weighing bottle that had been dried for 30 min under the same condition to be employed in the determination .Weighed the empty bottle (W1) .Put the sample in the bottle , replaced the cover, & accurately weighed the bottle & the content (W2) .By gentle, sidewise shaking ,distributed the sample as evenly as practicable to a depth of about 5 mm. placed the loaded bottle in the drying chamber . Dried the sample at the specified temperature for constant weight. Upon opening the chamber, closed the bottle promptly,& allowed it to come to room temperature in a desiccators before weighing .Weighed the bottle (W3) .The difference between successive weights should not be more than 0.5 mg .The loss on drying is calculated by the formula

$\%LOD = (W2-W3)/(W2-W1)\times100$

B. Solubility –

A semi-quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition , the system was vigoroudsly shken & examined visually for any undissolved solute particles. The solubility is expressed in turns of ratio of solute.

Table No.5 – Solubility & corresponding quantity of parts of solute.

Solubility	Mililitre/gm
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000 – 10,000
Practically insoluble	More than 10,000

pH – Weighed & transferred accurately about 1 gm of sample in a 20 ml clean & dried volumetric flask , dissolved in carbon dioxide free water & made up the volume to 20 ml with same solvent mixed. Determined the pH of freshly prepared solution by using precalibrated pH meter.

C. IR Spectroscopy

The IR spectrums of the sample & of the Lisinoprile dihydrate working / reference standard in the range of 4000cm^{-1} o 400 cm^{-1} were taken by preparing dispersion in dry potassium bromide under the same operational conditions. Superimposed these spectra .The transmission minima (absorption maxima) in the spectrum obtained with the sample corresponded in position & relative size to those in the spectrum obtained with the Lisinoprile dihydrate working /reference standard.

Compatibility studies

FT-IR spectroscopy was carried out to check the compatibility between drug and polymer. The FT-IR spectra of drug with polymers were compared with the standard FT-IR spectrum of the pure drug.

Immediate Release Layer

Standard calibration curve of Famotidine –

Preparation of calibration curves:

The standard curves in at pH 6.8.

Determination of λ_{max} (215nm)in pH 6.8

- Preparation of Potassium dihydrogen phosphate (0.2 M) solution. (Indian Pharmacopoeia, 2007)

Potassium dihydrogen phosphate (27.218 g) was dissolved in water and made the volume with water to 1000 ml.

- Preparation of Sodium hydroxide (0.2 M) solution

Sodium hydroxide (8 gm) was dissolved in 1000 ml water.

- Preparation of Phosphate buffer

In 200 ml volumetric flask, Potassium dihydrogen phosphate (50 ml, 0.2 M) was taken and to this solution Sodium hydroxide (22.4 ml, 0.2 M) was added and made the volume with water.

Preparation of stock solutions:

Weighed accurately 50 mg of Famotidine and dissolved in a few ml of phosphate buffer in a 100 ml volumetric flask. Then the volume was made up to 100 ml with Phosphate Buffer which gives 1 mg/ml concentration (Stock A). From that 10 ml solution was taken and dissolved in a few ml of phosphate buffer in a 100 ml volumetric flask. Then the volume was made up to 100 ml with the phosphate buffer, which gives 100 µg/ml concentrations (Stock B).

From the second stock solution 2, 4, 6,8, …… ,28, 30 µg/ml dilution was prepared. The absorbance of each sample was measured at 215 nm against blank mixed phosphate buffer. Standard curve of concentration (µg/ml) Vs absorbance was plotted.

Preparation of granules by wet granulation for different batches of immediate release : 1. Sifting: Solid dispersion (Etoricoxib and Poloxomer 188) (1:3) ratio, Sodium Starch Glycolate and Lactose were sifted through 40 sieve.

2. Binder Addition: Starch binder was added to the sifted powder.

3. Granulation: All the sifted ingredients were sifted to motar pestle and granules were prepared by adding 1-2 drops of distilled water in the sifted powder.

4. Drying: Granules were dried in hot air oven at 20°C till loss of drying of 1.5-2% is achieved.

5. Sizing: Dried granules were passed through 20 sieve.

6. Lubrication: Addition of intra-granulation material were sifted through 60# sieve and added to step 4 and mixed for 2 minutes.

7. Compression: The tablets were prepared by using single punch machine.

Famotidine layer formulation comprises of:

- 5%w/w concentration of Starch paste as a binder to get optimum blend flow properties and tablet hardness.
- 45.45%w/w concentration of HPMC K100M as a sustained release polymer to get desire drug dissolution upto 12Hrs.
- 10%w/w concentration of Sodium Bicarbonate as a gas generating agent to float the tablet with minimum floating lag time of 243 secs.
- Prototype formulation can be obtained by sustained release polymer (HPMC K100M), Effervescent concentration (Sodium Bicarbonate) and Binder concentration (Starch Paste) in range of 50mg to 150mg, 10mg to 30mg and 6mg to 12mg respectively using wet granulation method.
- Immediate release Vildagliptin layer shows that HPMC K100M, Sodium Bicarbonate and Starch Paste in concentration of 100mg, 22mg and 8.5mg respectively gives desired drug product quality attributes and these designed space was confirmed by taking confirmatory batches.

Table No. 6 : Flow Property Of Granules :

Flow Property	Bulk Density	Tapped Density	Carr's Compressibility Index	Hausner's Ratio	Angle Of Repose
Good	**0.431±0.73**	**0.519±0.50**	**16.18±0.14**	**1.19±0.32**	**23.18±0.09**

Table No. 7 : Formula for immediate release layer:

Ingredients (Mg)	G1	G2	G3
Famotidine	20	20	20
Cross carmellose Na	8	12	15
MCC	19.5	15.5	12.5
Mg Stearate	2.5	2.5	2.5
Total	50	50	50

Sustained Release Drug

Standard calibration curve of Clindamycin –

Preparation of calibration curves:

The standard curves in at pH 7.2.

Determination of λ_{max} (210nm) in pH 7.2.

- Preparation of Potassium dihydrogen phosphate (0.2 M) solution. (Indian Pharmacopoeia, 2007)

Potassium dihydrogen phosphate (27.218 g) was dissolved in water and made the volume with water to 1000 ml.

- Preparation of Sodium hydroxide (0.2 M) solution

Sodium hydroxide (8 gm) was dissolved in 1000 ml water.

- Preparation of Phosphate buffer

In 200 ml volumetric flask, Potassium dihydrogen phosphate (50 ml, 0.2 M) was taken and to this solution Sodium hydroxide (22.4 ml, 0.2 M) was added and made the volume with water.

Preparation of stock solutions:

Weighed accurately 50 mg of Clindamycin and dissolved in a few ml of phosphate buffer in a 100 ml volumetric flask. Then the volume was made up to 100 ml with Phosphate Buffer which gives 1 mg/ml concentration (Stock A). From that 10 ml solution was taken and dissolved in a few ml of phosphate buffer in a 100 ml volumetric flask. Then the volume was made up to 100 ml with the phosphate buffer, which gives 100 µg/ml concentrations (Stock B).

From the second stock solution 10,20,30,……..,80,90 µg/ml dilution was prepared. The absorbance of each sample was measured at 210 nm against blank mixed phosphate buffer. Standard curve of concentration (µg/ml) Vs absorbance was plotted.

Preparation of granules by wet granulation for different batches of sustained release:

The sustained release layer was also prepared by wet granulation technique.

1. Sifting: Microcrystalline Cellulose were shifted through 40 # sieve.

2. Binder Addition: Hydoxypropyl methyl cellulose (HPMC) was added to shifted powder.

3. Granulation: All the sifted ingredients were sifted to motar pestle and granules were prepared by adding 1-2 drops of distilled water in the sifted powder.

4. Drying: Granules were dried in hot air oven at 40°C till loss of drying of 1.5-2% is achieved.

5. Sizing: Dried granules were passed through 20 sieve.

6. Lubrication: Addition of intra-granulation material were sifted through 60# sieve and added to step 4 and mixed for 2 minutes.

7. Compression: The tablet were prepared by using single punch machine.

Table No. 7 : Flow Property Of Granules :

Flow Property	Bulk Density	Tapped Density	Carr's Compressibility Index	Hausner's Ratio	Angle Of Repose
Good	**0.541±0.63**	**0.509±0.40**	**16.16±0.15**	**1.15±0.43**	**22.18±0.10**

Table No. 8 : Formula for sustained release layer:

Ingredients	**M1**	**M2**	**M3**
Clindamycin	150	150	150
HPMC K4M	50	-	-
HPMC K15M	-	50	-
HPMC K100M	-	-	50
MCC	46	31	46
Starch	10	10	10
Mg Stearate	4	4	4
Ethanol	q.s.	q.s.	q.s.
Total	250	250	250

Famotidine IR Layer

↓

Dispensing

Clindamycin SR Layer

↓

Dispensing

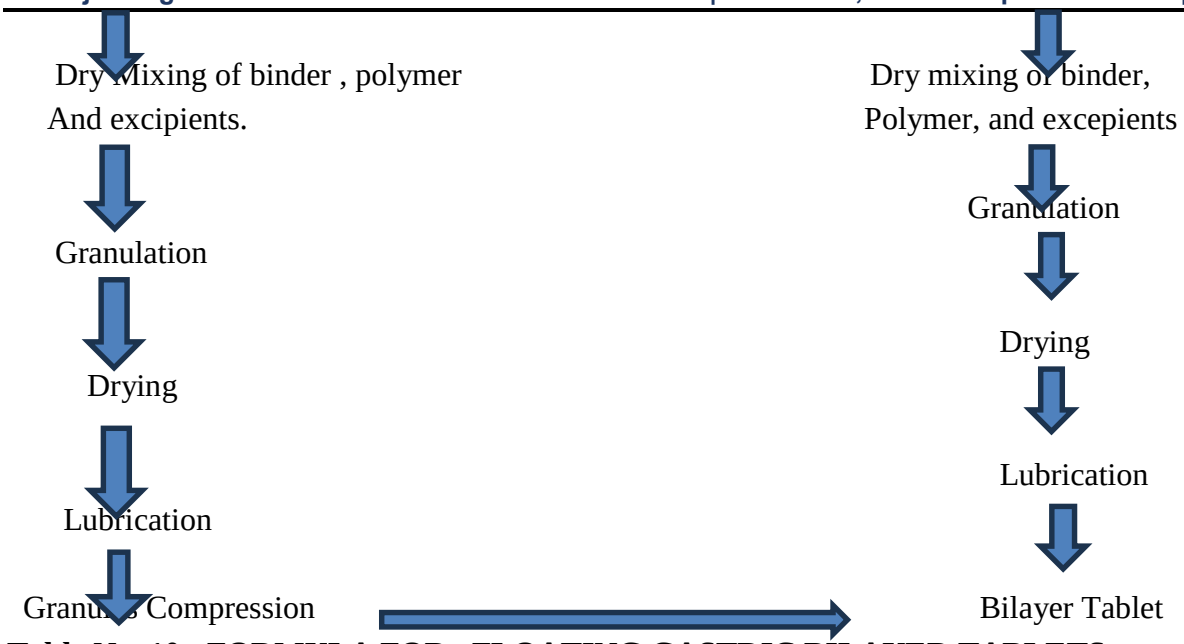


Table No. 10 : FORMULA FOR FLOATING GASTRIC BILAYER TABLETS:

Sr.no	Ingredients	B1	B2	B3	Ingredients (mg)	G3
1	Clindamycin	150	150	150	Famotidine	20
2	HPMC K4M	50	-	-	Cross carmellose Na	15
3	HPMC K15M	-	50	-	MCC	12.5
4	HPMC K100M	-	-	50	Mag. Stearate	2.5
5	Tartaric acid	56	46	36		
6	Starch	10	10	10		
7	Mag. Stearate	04	04	04		
8	Ethanol	q.s.	q.s.	q.s.		
9	Sod. bicarbonate	50	60	70		
10	Total	300	300	300		50

QUALITY CONTROL

Forming checks -

a)Weight variation

Ten tablets from each formulation were weighed using an electronic digital balance and the average weight was calculated.

Weigh individually 20 tablets & calculated the average weight : the weights of not more than 2 of the tablets differ from the average weight by more than the % listed & no. tablets differs by more than double that %..

b)Thickness

Tablets were evaluated for their thickness using slide calipers.

c) Drug content & content uniformity.

Ten tablets from each formulation were taken, crushed and mixed. From the mixture, 10 mg of Lisinoprile dihydrate equivalent of mixture was extracted thoroughly with 100 ml of methanol. The amount of drug present in extract was determined using UV Spectrometer at 210 nm.

d) Product release

The United States of Pharmacopoeia (USP) XXIV rotating paddle method was used to study the drug release from the bilayer . The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at 37oC ± 0.5oC, with rotation speed of 50 rpm. Samples (5ml) were withdrawn at predetermined time intervals (2,4 and 6…10 min) and volume was replaced with the fresh medium. The samples were filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at 210 nm.

The experiments for different formulations were conducted in triplicate and average values were recorded and found the release kinetics such as zero order, first order, Higuche and Hixconcrowell were determined.

e) Drug diffusion study – Diffusion cell apparatus was used to study the diffusion of the drug from the buccal mucosa of goat. The goat buccal mucosa was cut in appropriate size to fit into the cell.freshly cut buccal mucosa was used. The dissolution medium consisted of 6 ml of phosphate buffer (pH 6.8). The diffusion was performed at 37oC ± 0.5oC, with rotation speed of 50 rpm. Samples (1 ml) were withdrawn at predetermined time intervals (2,4 and 6…20 min) and volume was replaced with the fresh medium. The samples were filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at 210 nm.

Table No. 11: Drug diffusion study

Apparatus	Diffusion cell
Dissolution medium	Phosphate buffer (pH 6.8)
Temperature	37 ± 0.5 °C
Volume	6 ml
Speed	50 rpm
Sample withdrawn	1 ml
Running Time	20 min

f) Floating Time Study :

Floating Time study, also known as Floating Time Test or Buoyancy Study, is an in vitro evaluation method used to assess the floating properties of floating bilayer tablets (FBTs). The study aims to determine the time it takes for the tablet to float on a simulated gastric fluid.

Methodology:

1. Prepare a simulated gastric fluid (SGF) with a pH similar to the human stomach (typically pH 1.2).
2. Add a dye or marker to visualize the fluid.
3. Place the FBT in the SGF.
4. Record the time taken for the tablet to:
   - Float to the surface (Floating Lag Time, FLT).
   - Remain floating (Floating Time, FT).
   - Disintegrate or lose buoyancy.

Parameters evaluated:

1. Floating Lag Time (FLT): Time taken for the tablet to float to the surface.
2. Floating Time (FT): Duration the tablet remains floating.
3. Total Buoyancy Time (TBT): Sum of FLT and FT.
4. Buoyancy Percentage: Percentage of tablets that float within a specified time.

Acceptance criteria:

1. FLT: Typically ≤ 1 minute.
2. FT: Typically ≥ 4-8 hours (depending on the intended release profile).
3. TBT: Typically ≥ 4-12 hours.

RESULTS AND DISCUSSION

PREFORMULATION STUDY

a. Identification of pure drug

The IR spectrum of pure drug was found to be similar to the reference standard IR spectrum of Famotidine and Clindamycin

b. Organoleptic properties

1. Famotidine

Sr.no.	Description	Result
1.	**Appearance**	**White to pale yellow crystals**
2.	**Odour**	**odourless**
3.	**Solubility**	**Free Soluble in glacial acetic acid**

2.Clindamycin

Sr.no.	Description	Result
1.	**Appearance**	**White crystalline powder**
2.	**Odour**	**odourless**
3.	**Solubility**	**Soluble in water**

c. Melting point determination

The melting point of Famotidine and Clindamycin was found to be in the range of 163.5°C and 141-143 °C respectively.

d. Micromeritic study

1.Famotidine

Property Studied	Loose Bulk Density (g/ml)	Tapped Bulk Density(g/ml)	Carr's Index (%)	Hausner's Ratio (%)	Angle of Repose (ϕ)
Result	0.416±0.006	0.75±0.05	16.80±0.41	1.20±0.01	37±0.01

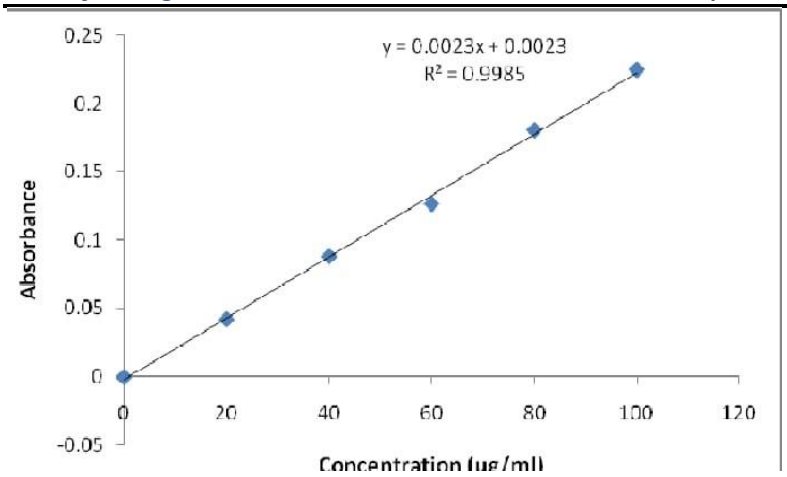
2.Clindamycin

Property Studied	Loose Bulk Density(g/ml)	Tapped Bulk Density(g/ml)	Carr's Index (%)	Hausner's Ratio (%)	Angle of Repose(ϕ)
Result	0.403±0.01	0.490±0.02	17.75±0.12	1.22±0.02	27.34±0.57

ANALYTICAL METHOD OR CALIBRATION CURVE

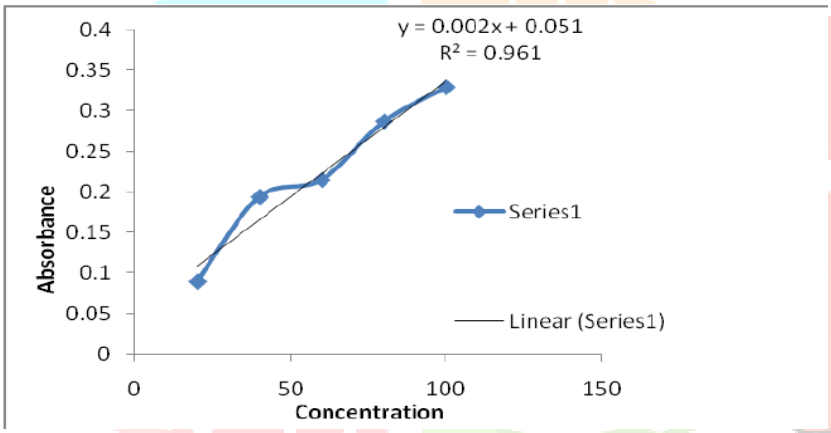
Famotidine

1. Calibration curve in Phosphate buffer (pH 6.8)



Parameters	value
Λmax	**215nm**
R^2	**0.9985**
Equation of line	**Y = 0.0023*+0.0023**
Con. Range	**2-38µg/ml**

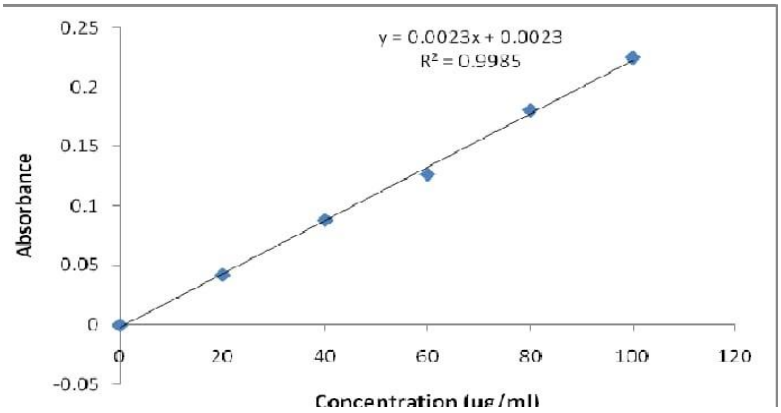
2. Calibration curve in 0.1N Hydrochloric acid



Parameters	value
Λmax	**215nm**
R^2	**0.961**
Equation of line	**Y = 0.002x+0.051**
Con. Range	**2-39µg/ml**

Clindamycin

1. Calibration curve in Phosphate buffer (pH 7.2)

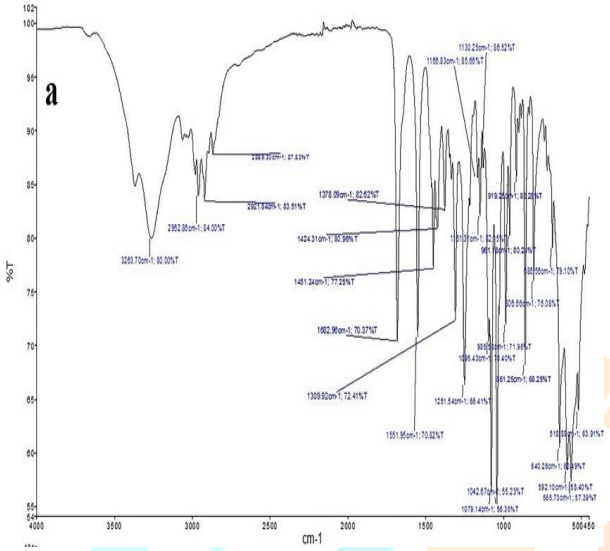


Parameters	value
Λmax	**210nm**
R^2	**0.9985**
Equation of line	**Y = 0.0023*+0.0023**
Con. Range	**2-40µg/ml**

COMPATIBILITY STUDY OF INGREDIENTS (DRUG & EXCIPIENTS)

1. Sustained release layer

Clindamycin

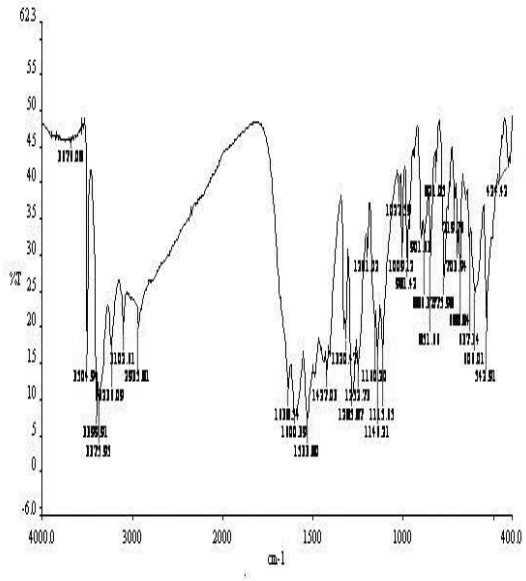


Ranges of Fun. Group of Clindamycin

Range (cm^{-1})	Functional gr. present
782-929	C-N
1037-1261	C-N
1515-1662	N-H deformation
3267-3378	NH_2
3502-3729	-NH streching

2. Immediate release layer

Famotidine



Ranges of fun. Group of Famotidine

Range (cm^{-1})	Functional group present
800 – 914	-NH
1160 – 1349	C – H aromatic
1700 – 1800	Sulphonyl urea
1706 – 1780	C = O aromatic
3000 – 3100	C - H

FORMULATION DEVELOPMENT

1. Pre compressional Study of Tablet

a. Sustained release layer

Property	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose(ϕ)
M1	0.482±0.04	0.50±0.05	3.7±0.28	1.03±0.02	28.33±1.2
M2	0.513±0.05	0.533±0.04	3.8±0.3	1.04±0.5	26.12±1.8
M3	0.470±0.03	0.487±0.02	3.45±0.08	1.03±0.02	22.34±0.2

b. Immediate release layer

Property Batches	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausners ratio	Angle ofrepose (ϕ)
G1	0.414±0	0.450±0.02	8±0.5	1.08±0	28.45±0.5
G2	0.418±0.005	0.478±0.03	12.55±0.1	1.14±0.04	27.56±0.4
G3	0.421±0.01	0.487±0.02	13.55±0.4	1.156±0.05	25.21±0.8

2. Post compressional study

a. Sustained release layer

Property Batch	Diameter (mm)	Thickness (mm),	Hardness (kg/cm^2),	Weight Variation (mg)	Friability (%)	Drug Content (%),
M1	17	5.01±0.1	5.83±0.1	752.0±1	0.55	94.35±0.9
M2	17	5.2±0.17	5.63±0.3	751.85±0	0.79	94.01±0.005
M3	17	5.1±0.05	6.96±0.18	749.3±1	0.12	96.27±0.5

b. Immediate release layer

Property Batch	Thickness (mm),	Hardness (kg/cm^2),	Weight Variation(mg)	Friability (%)	Drug Content (%),
G1	2.45±0.01	4.1±0.2	304.55±0.5	0.132	96.05±0.72
G2	2.51±0.02	4.26±0.2	304.1±0.8	0.28	95.19±0.65
G3	2.57±0.03	3.96±0.2	305.8±0.3	0.28	97.16±0.72

Evaluation tests

The formulated tablets were subjected for the quality control tests such as weight variation, hardness, friability, drug content uniformity, disintegration, in-vitro dissolution studies.

Property / Batch	Diameter (mm)	Thickness (mm),	Hardness (kg/cm^2),	Weight Variation (mg)	Friability (%)	Drug Content (%),
M1	17	5.01±0.1	5.83±0.1	752.0±1	0.55	94.35±0.9
M2	17	5.2±0.17	5.63±0.3	751.85±0	0.79	94.01±0.005
M3	17	5.1±0.05	6.96±0.18	749.3±±1	0.12	96.27±0.5

Table 3: Evaluation tests of Clindamycin sustained release tablets

Property / Batches	Thickness (mm),	Hardness (kg/cm^2),	Weight Variation(mg)	Friability (%)	Drug Content (%),
G1	2.45±0.01	4.1±0.2	304.55±0.5	0.132	96.05±0.72
G2	2.51±0.02	4.26±0.2	304.1±0.8	0.28	95.19±0.65
G3	2.57±0.03	3.96±0.2	305.8±0.3	0.28	97.16±0.72

Table 4: Evaluation tests of Famotidine immediate release tablets

In-vitro dissolution study

The two intact tablets from each batch were taken for dissolution study. The dissolution study was performed in IP-II (Basket) / USP Type-I dissolution test apparatus (Electrolab, TDT 08L, Mumbai, India). The dissolution medium used was 900 ml of 0.1N HCl for first 2 hours and phosphate buffer (pH 7.4) for next 10 hrs at 37 ± 0.7 °C. The paddle speed was kept constant at 50 rpm. Each time, 5 ml of sample were withdrawn at the interval of 5 min for Gliclazide and 2 ml sample were withdrawn for Metformin Hydrochloride, for first 1 hour and thereafter at interval of 1hr. The withdrawn samples were analyzed spectrophotometrically at 230nm for Gliclazide and 233 for Metformin Hydrochloride. The same amount of fresh 0.1 N HCl and phosphate buffer pH 7.4 was used to replace the amount withdrawn for respective dissolution media. Percent cumulative release of both drugs from the tablet was calculated.

1. For Clindamycin :

Sr.No.	Time (Hrs)	% Drug Release		
		M1	M2	M3
0	0	0	0	0
1	30	15.54	16.15	14.22
2	60	27.12	28.13	25.09
3	90	46.72	48.14	42.35
4	120	56.58	58.20	52.21
5	150	68.66	70.49	65.62
6	180	80.65	82.68	74.96
7	210	89.59	90.30	83.70
8	240	91.72	91.82	88.78
9	270	88.37	89.79	92.84
10	300	-	-	90.60

Table 5: In vitro drug release for formulation (M1-M9)

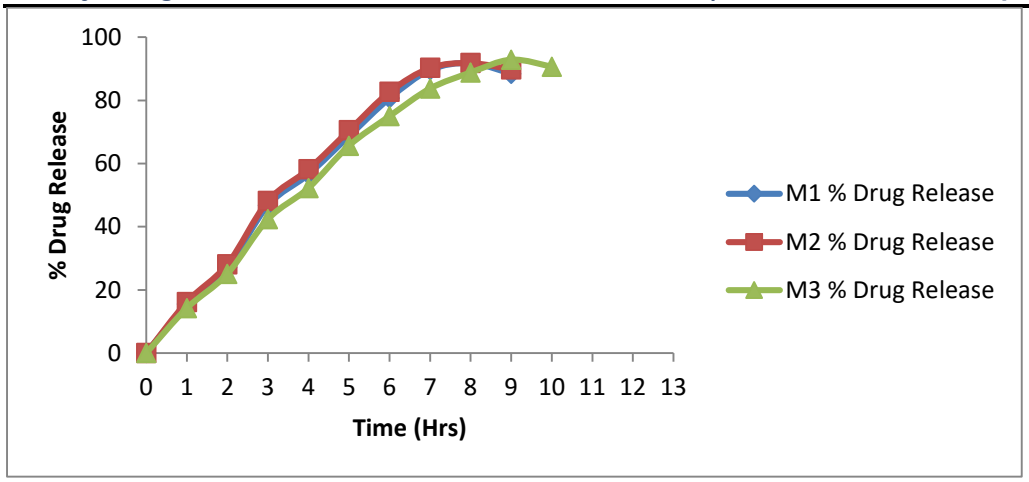


Fig.3: In Vitro drug release pattern of formulation M1-M3

From above comparative in vitro drug release it is concluded that above formulated formulations M1-M9 in which M9 formulation gives stable and more sustained drug release, so M9 containing HPMC K100M gives more optimise and sustained drug release pattern from the above formulations as compared to HPMC K4M and K15M.

2. For Famotidine :

Sr.No.	Time (min)	% Drug release		
		G1	G2	G3
1	05	52.64	50.33	51.49
2	10	59.45	62.69	80.58
3	15	75.16	83.24	92.47
4	20	88.32	92.82	93.40
5	25	93.13	94.55	95.59

Table 6: *In Vitro* drug release pattern of formulation G1-G3

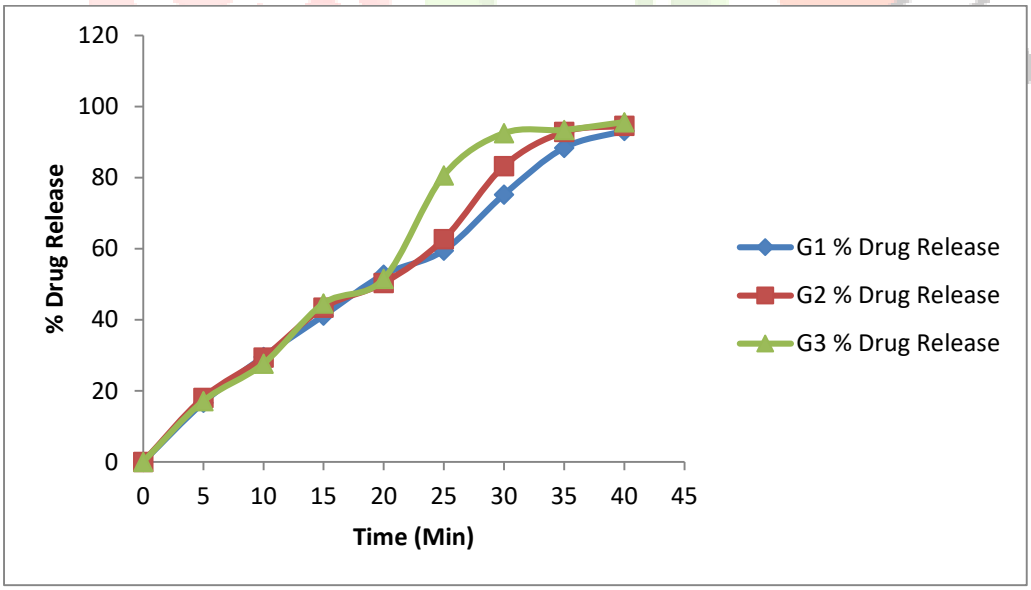


Fig.7: Comparative In vitro dissolution pattern of Famotidine G1-G3

From above comparative in vitro drug release it is concluded that above formulated formulations G1-G3 in which G3 formulation gives burst release effect, because of it contains more amount of super disintegrant.

Preparation of Final Floating Bilayer tablets

Optimized formulations of Metformin hydrochloride SR tablets and Gliclazide IR tablets were selected and final bilayer tablets were prepared. Metformin layer was slightly compressed and then IR tablet powder was added and compressed together to get the final bilayer tablet.

Sr.no	Ingredients	B1	B2	B3	Ingredients (mg)	G3
1	Clindamycin	150	150	150	Famotidine	20
2	HPMC K4M	50	-	-	Cross carmellose Na	15
3	HPMC K15M	-	50	-	MCC	12.5
4	HPMC K100M	-	-	50	Mag. Stearate	2.5
5	Tartaric acid	56	46	36		
6	Starch	10	10	10		
7	Mag. Stearate	04	04	04		
8	Ethanol	q.s.	q.s.	q.s.		
9	Sod. bicarbonate	50	60	70		
10	Total	300	300	300		50

Table 7: Formulation of Floating Bilayer Tablets

Evaluation of Floating bilayered tablet:

	B1	B2	B3
Thickness (mm)	**7.37±0.05**	**7.52±0.11**	**7.63±0.2**
Hardness (kg/cm^2)	**5.84±0.5**	**6.01±0.01**	**6.3±0.1**
Weight variation (mg)	**1054.35±0.5**	**1055.15±0.8**	**1050.8±1.41**
Friability (%)	**0.592**	**0.471**	**0.50**
Drug Content (%) **Metformin Hcl** **Gliclazide**	 **97.33±1** **96.33±1**	 **98.21±0.21** **95.21±1.1**	 **96.35±1** **96.22±0.78**
Floating time	**2 hr**	**2 hr 50 min**	**3 hr 2 min**

Table 8: Evaluation parameter of floating Bilayer formulations B1-B3

In vitro dissolution study of bilayer tablets:

Three tablets from each batch of bilayer tablet were subjected to dissolution testing. The % cumulative release of both drugs was calculated. Dissolution medium was 0.1N HCl for first 2 hours and phosphate buffer (pH7.4) for next 10 hours.

1. For Clindamycin :

Sr.No.	Time (Hrs)	% Drug release		
		B1	B2	B3
0	0	0	0	0.00
1	30	15.22	12.75	8.89
2	1 hr	27.09	25.22	19.36
3	90	44.30	39.89	31.27
4	2 hr	54.21	49.75	42.25
5	150	64.62	60.26	53.28
6	3 hr	75.86	71.68	60.59
7	210	86.67	84.75	70.69
8	4 hr	89.71	92.94	81.06

9	270	93.92	94.91	86.93
10	5 hr	91.60	92.10	92.91

Table 9: In vitro dissolution study of bilayer tablets

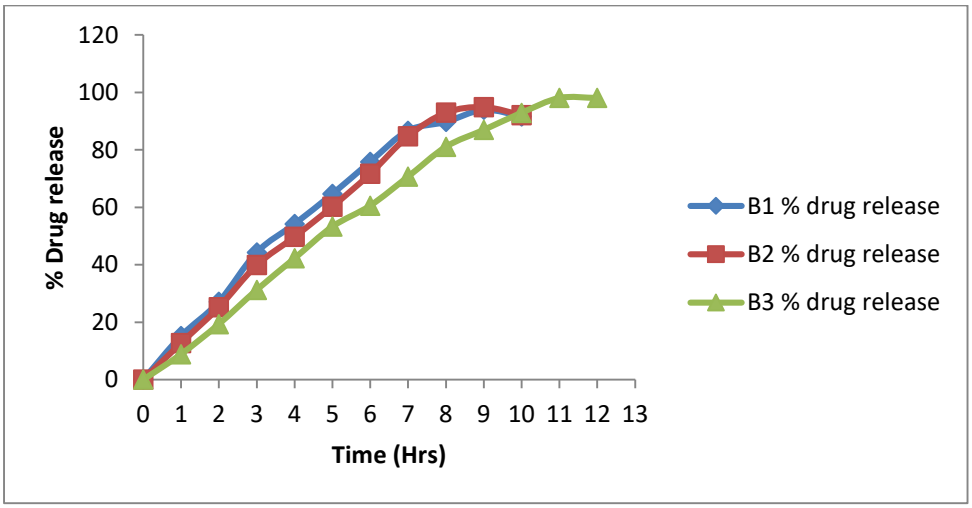


Fig.8: Comparative dissolution pattern of Bilayer Tablet containing Clindamycin B1-B3.

HPMC K100M gives more optimise and sustained drug release pattern from the above formulations as compared to HPMC K4M and K15M.

2. For Famotidine :

Sr. No.	Time (min)	% Drug release		
		B 1	B2	B3
1	0	0	0	0
2	05	16.58	19.65	17.08
3	10	26.48	26.98	27.59
4	15	44.10	43.54	44.56
5	20	51.0	50.25	51.49
6	25	78.48	79.25	80.58
7	30	92.11	91.89	92.47
8	35	93.02	92.89	93.04
9	40	93.89	94.58	93.59

Table 10: Comparative dissolution pattern of Bilayer Tablet containing Famotidine B1-B3.

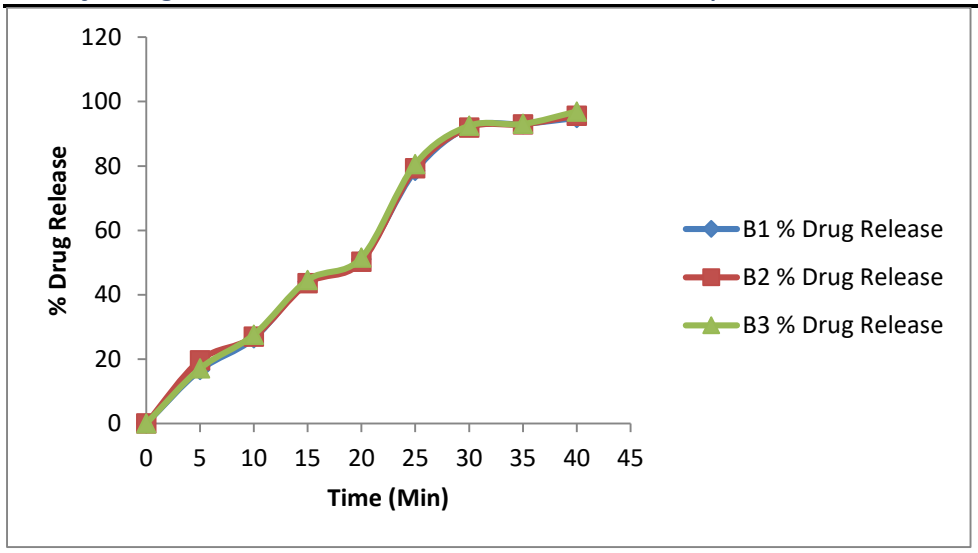


Fig.9: Comparative dissolution pattern of Bilayer Tablet contaning Famotidine B1-B3.

CONCLUSION

HPMC used as matrix forming polymer for the Clindamycin layer enables drug release for up to 9-10 hours. Among the different grades of HPMC there is significant difference in the resulting Clindamycin release profiles from the SR layer of the tablets was found. The formulation M3 can be preferred as integrity was maintained.

Famotidine release shows that the dissolution rate of Famotidine can be enhanced considerably by formulating it as a solid dispersion with PEG 6000 using solvent evaporation method. Incorporation of super disitnegrants in the formulation played a critical role in dissolution rate enhancement.

REFERENCE

1. Tejaswi Santosh Ubhe1, Preeti Gedam, A Brief Overview on Tablet and It's Types , Journal of Advancement in Pharmacology,2020, ,Volume 1 Issue 1 , (Page 21–31)

2. Introduction to Tablet, Capsule and Its Different ,Evaluation techniques ,
Ms. Pooja S Murkute, Mr.Ankush G Pawar, Mr. Nakul P Kathar, Dr. Gajanan S Sanap, Mr. Shekhar Pandav, Ms. Aishwarya P Pimple
2022 IJCRT , Volume 10, Issue 7 July 2022.

3. FORMULATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF FAMOTIDINE
B K Satishbabu , V R Sandeep , R B Ravi , R Shrutinag , Indian J Pharm Sci
. 2010 Nov-Dec;72(6):738–744

4 . FLOATING DRUG DELIVERY SYSTEM: A REVIEW Vishal Bhardwaj*, Nirmala, S.L. Harikumar Rayat and Bahra Institute of Pharmacy, Sahauran, Kharar, Mohali, Punjab , Pharmacophore (An International Research Journal) , Pharmacophore 2013, Vol. 4 (1), 26-38.

5.Formulation and Evaluation of Floating Drug Delivery System of Famotidine, B K Satishbabu , V R Sandeep , R B Ravi , R Shrutinag , Indian J Pharm Sci. 2010 Nov-Dec;72(6):738–744.

6. FLOATING GASTRORETENTIVE DRUG DELIVERY SYSTEMS: COMPARISON OF EXPERIMENTAL AND SIMULATED DISSOLUTION PROFILES AND FLOATATION BEHAVIOR
Author links open overlay panelVeronika A. Eberle , Joachim Schoelkopf , Patrick A.C. Gane , Rainer Alles , Jörg Huwyler , Maxim Puchkov , European Journal of Pharmaceutical Sciences, Volume 58, 16 July 2014, Pages 34-43.

7 . Review article overview on floating drug delivery system, mirmeera girish niharika, kannan krishnamoorthy, madhukar akkala , Avanthi Institute of Pharmaceutical Sciences, JNTUH, Hyderabad, Telangana, India, Department of Pharmacy, Annamalai University, Annamalai Nagar, Tamilnadu, India, International Journal Applied Pharmaceutics , Vol 10, Issue 6, 2018.

8 . Floating Drug Delivery System: A Brief Review ,Haridwar Lodh, Sheeba FR, Prabhat Kumar Chourasia, Harshitha Arun Pardhe, Pallavi N , Asian J. Pharm. Tech. 2020; 10(4):255-264.

9 . Overview on floating drug delivery system

Mirmeera girish niharika, kannan krishnamoorthy, madhukar akkala

Avanthi Institute of Pharmaceutical Sciences, JNTUH, Hyderabad, Telangana, India, Department of Pharmacy, Annamalai University, Annamalai Nagar, Tamilnadu, India.

Received: 26 Jul 2018, Revised and Accepted: 04 Oct 2018.

10 . Bilayer tablets: A developing novel drug delivery system,Muneeba Akhtar , Muhammad Jamshaid , Muhammad Zaman , Agha Zeeshan Mirza, Journal of Drug Delivery Science and Technology , Volume 60, December 2020.

11 . A Review on Bi-layer Tablets M. Namrata*, V.N.L. Sirisha, B. Sruthi, I. Bhavani Harika, P.Kirankumar, Y.Kiran Kumar Rao, K.Pranavi, S.Sindhura, N.Vamsi Krishna, O. UmaMaheshwara Rao , Int.J.Pharm.Phytopharmacol.Res. 2013, 2(4): 240-246

12 . An overview on bilayered tablet technology, C. Gopinath, V. Hima Bindu, abstract M. Nischala , Department of Pharmaceutical Technology, Annamacharya College of Pharmacy, Rajampet, 516126, (A.P) INDIA. Journal of Global Trends in Pharmaceutical Sciences Volume 4, Issue 2, pp -1077-1085, April- June 2013.

13 . RECENT APPROACHES OF BILAYER TABLET TECHNOLOGY: A REVIEW Miss. Pratibha K. Pagar* , Prof. Mitesh P. Sonawane, Miss. Aishwarya G. Bhamare, Miss. Shamal S. Patil, Miss. Vaishali V. Pagar , 2023 IJCRT | Volume 11, Issue 2 February 2023.

14 . Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension Balaji Maddiboyina , Mudavath Hanumanaik , Ramya

Krishna Nakkala , Vikas Jhawat , Pinki Rawat , Aftab Alam , Ahmed I. Foudah , Majed M. Alrobaian , Rahul Shukla , Sima Singh , Prashant Kesharwani , Volume 6, Issue 11, November 2020

15 . Bilayer Floating Tablet: A Novel Pharmaceutical Approaches for Gastroretention

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Submission: September 1, 2021; Published: September 27, 2021

16. A review on bilayer floating tablets: a new trend kothuri jyothi, karre supriya, ch. Shanthi priya, s. Rohini reddy , international journal of current advanced research , volume 13; issue 04; april 2024; page no.3039-3044.

17 . Bilayer Floating Tablet: A Novel Pharmaceutical Approaches for Gastroretention

Deepika Joshi, Kamal Kaushik ,Bhavana Singh , Nidhi Semwal

School of Pharmaceutical Sciences, SGRR University, Dehradun, 248001, India

Submission: September 1, 2021; Published: September 27, 2021

18] A Comprehensive Review on Floating Drug Delivery System Natasha Sharma, Dilip Agarwal, M.K. Gupta and Mahaveer Pr. Khinchi. Apr – Jun 2011. Department of Pharmaceutics, Kota College of Pharmacy, Kota, Rajasthan, India. Vol. 2 (2) Apr – Jun 2011

19] A Critical Review on Floating Tablets as a Tool for Achieving Better Gastric Retention.Volume 39, Issue 1, 2022, pp. 65-103 Anjali Rajora, Kalpana Nagpal

20] Floating Drug Delivery Systems: A Review S. Gopalakrishnan and A. Chenthilnathan Department of Pharmaceutical Chemistry, Manonmaniam Sundaranar University. S.Gopalakrishnan et al / Journal of Pharmaceutical Science and Technology Vol. 3 (2), 2011,548-554

21] Formulation and Evaluation of Floating Dosage Forms: An Overview. Authors Sabale, V.; Sakarkar, S. N.; Pund, S.; Sabale, P. M. Publication Systematic Reviews in Pharmacy, 2010, Vol 1, Issue 1, p33

22] An overview of a gastro-retentive floating drug delivery system S. H. Shaha, J. K. Patel , K. Pundarikakshudu , N. V. Patel . Gastro-retentive floating drug delivery system/Asian Journal of Pharmaceutical Sciences 2009, 4 (1): 65-80

Received 17 June 2008; Revised 29 October 2008; Accepted 3 January 2009

23] FLOATING BILAYER TABLET: A REVIEW

Saliya Parveen, R. B. Nawale, Sadhana Shahi, Nityanand S. Zadbuke and Shehla Khan , Department of Pharmaceutics, Government College of Pharmacy, Osmanpura, Aurangabad 431005, Maharashtra. European Journal of Pharmaceutical and Medical Research. ejpmr, 2018,5(1), XXX-XXX

Article Received on 16/11/2017

Article Revised on 06/12/2017

Article Accepted on 26/12/2017

24] A brief review on bilayer floating tablet Kumari Roshani , Prabhudutta Panda, D.K. Vishwakarma and Navneet Kumar Verma, Department of Pharmaceutics. Shubha Srivastava et al / International Journal of Advances in Pharmaceutics 2017; 06(03): 70-78

25] Bilayer tablets- a review.

Kiran, B. Siva Sai; Rao, P. Sambasiva; Babu, G. Raveendra; Kumari, M. Venkat Publication : International Journal of Pharmaceutical, Chemical & Biological Sciences, 2015, Vol 5, Issue 3, p510

30] Bi-layer tablets for various drugs: A review Verma Rameshwar , Devre Kishor, Gangrade Tushar. Scholars Academic Journal of Pharmacy (SAJP) Sch. Acad. J. Pharm., 2014; 3(3): 271-279

31] Bilayer tablets: A developing novel drug delivery system

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Received 29 July 2020, Revised 15 August 2020, Accepted 3 September 2020, Available online 11 September 2020, Version of Record 16 September 2020.

32] Floating Drug Delivery Systems: An Emerging Trend for the Treatment of Peptic Ulcer , Namdev, Ankit; Jain, Dharmendra , Current Drug Delivery, Volume 16, Number 10, 2019, pp. 874-886(13)

33]Chremos AN: Clinical pharmacology of famotidine: a summary. J Clin Gastroenterol. 1987;9 Suppl 2:7-12. doi: 10.1097/00004836-198707002-00003. [Article]

34]Langtry HD, Grant SM, Goa KL: Famotidine. An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in peptic ulcer disease and other allied diseases. Drugs. 1989 Oct;38(4):551-90. doi: 10.2165/00003495-198938040-00005. [Article]

35] Donald E. Ayer, Carl A. Schlagel, Gordon L. Flynn, "Topical clindamycin preparations." U.S. Patent US4018918, issued January, 1971.

US4018918

*36]Leigh DA ,***Antibacterial activity and pharmacokinetics of clindamycin.**

J Antimicrob Chemother. 1981 Jun;7 Suppl A:3-9. doi: 10.1093/jac/7.suppl_a.3.

37]Plaisance KI, Drusano GL, Forrest A, Townsend RJ, Standiford HC: Pharmacokinetic evaluation of two dosage regimens of clindamycin phosphate. Antimicrob Agents Chemother. 1989 May;33(5):618-20. [Article]

37]Wynalda MA, Hutzler JM, Koets MD, Podoll T, Wienkers LC: In vitro metabolism of clindamycin in human liver and intestinal microsomes. Drug Metab Dispos. 2003 Jul;31(7):878-87. doi: 10.1124/dmd.31.7.878. [Article]

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