1. INTRODUCTION

1.1 Introduction to gastro – retentive solid oral dosage form and gastro resistance solid oral dosage form

1.1.1 Gastro retentive tablets

Tablet is common dosage form for the pharmaceutical industry. In the tablet there is active pharmaceutical ingredient and inactive pharmaceutical ingredients. These inactive pharmaceutical ingredients give strength and various release, chemical and physical stability, improve efficacy to the dosage form. And the active pharmaceutical ingredient give pharmacological action. In the inactive there are several lubricant, diluents, glidant, binder sweeteners are added. Lubricant and glidant improve flow property during tabletting, binder provide mechanical strength to the tablets, disintegrant ensure the break up of the dosage form in the invivo fluid, color and flavor enhance visual character and taste of the dosage form. Various polymer had been used for special purpose like to shape the dissolution profile and invivo release of active ingredient, to improve the tablets mechanical strength, its dinintegration property, tablets breaking force, improves shelf life and to give physical as well as chemical stability to the dosage form.

The orally administered dosage form is the more preferable dosage form which had high patient compliance, ease in uptake, cost effective. When the disease in chronic condition the orally administered dosage form for long term. The dosage form should be such that it can be easily administered, ease of absorption, throughout the gastrointestinal tract specially for the drug having less biological half life give its pharmacological action and quickly eliminate from the circulation. Thus, there is requirement of regulating the dosage unit to stay longer in the gastro environment and so required to design the modification of release of active content from dosage unit. By doing the modification in dosage form the release will be at specific site of action.

The active content that intended for gastro retentive systems are those which are absorbed form the stomach, having less solubility profile in the basic pH, having better absorption from the gastrointestinal tract, which degrade at various alkaline pH of the intestinal tract and later part of intestine.. Tablets having large appearance tablets are emptied during house keeping waves and the tablets that are small
dissolved during the gastic movement. Solid oral Floating dosage form remained buoyant on gastric fluids. Thus for these type of limitation floating dosage unit will be the most suitable.¹
Various system for gastric retention (Solid oral dosage form)²

There are different regulator which include modification of dosage form with the help of different polymers, different polymeric concentration, application of different property of the polymer. This modifies the release pattern and specific therapeutic action and pharmacological action of the particular dosage form. One of the type is floating drug delivery system.

Solid oral floating drug delivery systems

The formulation of this system depends on the density of the particular pharmaceutical dosage form. The intragastric floating property of dosage form will remain less as compare to intragastric liquid and thus it remains float on the upper side due to its floating property and remains in the gastrointestinal tract for extended period. The tablet will float at gastric condition and the active content will release slowly with modification in release pattern as desired. When all the active content released from the tablet the pharmaceutical dosage form will be removed from the respective area. So, such system regulate gastric retention period and also regulate variation in drug concentration at plasma level. There are two types of floating system i.e. effervescent floating system and Non effervescent floating system.

Non-effervescent systems:

There are different types of non effervescent floating system. These system includes Microporous compartment systems, Multi particulate system, Colloidal gel barrier systems, micro-balloons etc.

Microporous compartment systems

In this system the active content will not come in contact directly to the gastric environment. The outer layer of dosage is completely sealed. The Active content is sandwiched and around the dosage form there is micro aperture for availing the active content in the surroundings.
Multi particulate system

In these systems, the active content is sprayed or layered on small pellets mainly sugar spheres or microcrystalline cellulose spheres. Thus, the drug will be released from the discrete particle and at an extended period of time. The release pattern depends on the types of pellets, number of pellets, type of polymer used for coating, etc. In these systems, the drug will be released from a number of pellets and release depends on the surface area of the particle exposed.

Colloidal gel barrier systems

In this system, the active content is discharged from the dosage form at a required rate. The release pattern is controlled by various gel-forming hydrocolloids. These hydrocolloids have properties like swelling, wicking, gel forming, etc.

Microballoons

In this system, the active substance discharged from the dosage form with modification in release at specific site of action. In these dosage forms, an active substance is entrapped in porous microspheres. The microballoons will remain floating in the gastric environment depending upon the type of polymer used for the preparation of the same. From the different studies performed, it has been concluded that microballoons, when orally administered to humans, remain at the upper part of the stomach for three to four hours against the peristaltic movement of the stomach.

Effervescent systems (gas generating systems)

A dosage form can be made to remain buoyant at gastric conditions by using different systems that include:

1. Volatile liquid containing systems
2. Gas generating systems

Gas generating systems

The system basically works on the basic principle of medicinal chemistry. There is a reaction between acid and base, and due to this reaction, the gas evolves. Due to reaction and gas generation, the dosage form will lose its basic weight and remains
bouyant. Due to these the tablet will remain bouyant so, active content will dissolve slowly into the gastric environment and at specific site of action and perform its therapeutic activity. In these system acid and base used around eighty percent of the dosage form. Acid to be used includes tartaric acid, citric acid and base used in the system includes sodium carbonate, sodium bicarbonate etc. Beyond these there is usage of gel forming and release controlling polymer. Due to gel formation the specific gravity of system decrease and the dosage form floats. There are two types of floating system which included bi layer floating dosage form and Single layer floating tablets.

**Single layer floating dosage form:** In the single layer solid dosage form the tablet’s density is comparatively less when compared to the gastric fluid. So the dosage form float on the gastric fluid. In these formulation the active substance mix with gel forming polymer which reacts with gastric environment and swells and retain the density of the dosage form comparatively low to gastric fluids. Single layer floating dosage form are prepared by combination of active content with quite low density polymeric materials such as Hypromellose.

**Bilayer Floating Tablets**: In these type of dosage form there are two layers prepared with different rate of release or two different release profile. One layer releases fast then the other layer.
Brief discussion and mechanism about bilayer floating tablet:

![Diagram of Bilayer Floating Tablet]

**Figure. 1: Bilayer Floating Tablet**

**Types of bilayer tablet and its release pattern**

**Immediate release formulation**

The dissolution of active content from the conventional tablet form and its in vivo release from the Gastrointestinal tract depends upon two main processes. First, the disintegration of tablet into particulate and dissolution of these particulate through the Gastrointestinal tract into the blood. Disintegration time is the controlled step in case of drugs with having BCS class 1 and 3 while dissolution time is the controlled step in case of drugs with having BCS class 2 and 4.
Figure. 2: Rate limiting steps and its pattern in the absorption of drug from the Gastro intestinal tract\textsuperscript{3}.

The release of drug from an immediate release layer orodosage form can be achieved by

- Placing the drug in a layer or coating that is thin to allow fast penetration by gastrointestinal fluid which then leaches the drug at a fast rate.
- Incorporation of the drug in a mixture that includes a supporting binder or other inert material that dissolves rapidly and readily in gastrointestinal fluid, releasing the drug as the material solubilize or dissolves.
- Using supporting inert material or binder that disintegrates fast into fine particles upon contact with gastrointestinal fluid, with both the binder and the drug disperse quickly into the fluid.

Traditional dosage forms can be considered to release their active pharmaceutical ingredients into an absorption site immediately. The absorption pool represents a solution from the drug at the site of absorption. This is illustrated in the following scheme:
Mechanism of disintegrants
   a) High swellable
   b) Capillary action or wicking effect
   c) Chemical reaction

Extended release formulation
In the conventional dosage form the active substance release from the dosage form with controlled rate at specific site of action. These dosage form should be formulated in such a way that it should meet all the regulatory guideline in terms of safety, efficacy and stability. In most of the case the dosage form is bioequivalent and stable but some have less therapeutic index and are toxic in nature. In some case of dose dumping it is also harmful to the patient. So in such case there is need to maintain or regulate the dissolution profile of the active content from the tablets.

From figure 3 it had been revealed that the active content released from the dosage form had been illustrated for conventional drug delivery and controlled drug delivery.

![Diagram of drug levels in the blood with immediate and controlled release of active content from the dosage form.](image)

Figure. 3: Drug levels in the blood with immediate and controlled release of active content from the dosage form
Delivery of active substance from dosage form can be represented by mentioned equation as:
Desired drug level × Rate constant for drug elimination from the body x volume of distribution which is equal to rate in and also equal to rate out.

**Mechanism of active ingredient release through hydrophilic polymeric matrices**
Compressed hydrophilic matrices are more commonly used as modified release dosage form for oral administration. These matrices incorporate hydrophilic polymers which swell fast. Dissolution of active content from dosage form drug depends on the concentration and infusion of fluid in to the dosage form, the integrity of the gel forming layer and the diffusion of active content through the swollen polymeric matrices. Hypromellose is most commonly used in swellable matrix controlled systems because it tends to swell rapidly on absorption of water. Hypromellose being nonionic shows pH independent swelling. Hypromellose absorbs water as it enters and passes through the upper tract and substantially undergoes complete gel formation at least 70%. The structure of Hypromellose is linear and therefore it readily solublize in water. As the preparation continues down the Gastro Intestinal tract the cellulose ether solubilize, its surface gradually burst maintaining a controlled release of drug. Hypromellose when used shows an initial burst release. This may be controlled by combination with different polymer and its concentration.

**Selection of different polymeres**

a. **Gas generating agent**

**Acidifying agents and Basifying agents**

Acidifying agent includes Citric acid, tartaric acid, Adipic acid.
Basifying agent includes Sodium carbonate, sodium bicarbonate

**Rational behind the selection**

When acidifying and basifying agent comes in direct contact with gastric environment gas is generated and released in the acidic environment and trapped in the gelling layer and makes the density of dosage form quite less. So the dosage form floats in the gastric environment.
Acidifying agent is used as pH of stomach is increased after the administration of food to 4. Acidifying agent like citric acid gives lower pH to basifying agent as sodium carbonate and sodium bicarbonate.

b. **Viscosity increasing agent**

Sodium salt of alginate, different grades of carbopol

**Rational behind the selection**

Since the development stage there are different grade of carbopol used for modification in dissolution profile of the active content from the dosage form. There are various different carbopol for controlled release action from different suppliers. The product developed with different grade of Carbopol have shown zero order release kinetics. These can be utilized at very low proportions i.e. around 10% w/w of the formulation. By using these polymer they show accelerated swelling property at both stage when the dosage form enters at their specific site of action at acidic environment of gastric condition and basic environment of intestinal condition. These polymer when utilized give formulation with good physical attributes of the dosage form. The release profile of carbopol is also pH independent. By using these grade of polymer they show extension in release profile of active content from the dosage form but due to its property the polymer swells fast and give controlled effect of the dosage form. As the various grade of Carbopol absorb large quantity of purified water and it swell fast comparative to other polymer. Because of these property the dry mix of formulation is rarely feasible and dry granulation or wet granulation is the method of choice. So it can be concluded by these property of Carbopol polymer 71GNF is useful and efficacious sustained release polymer for addition in the formulation development.

**Drug solubilization mechanism from various grade of carbopol polymers**

When the different grade of carbopol utilized the active content trapped in the dosage form when the utilization done at the dry state. When media or fluid comes in contact of the external layer the external surface forms gel layer and the gel layer have its own release profile compare to traditional dosage form. The external layer of carbopol form is not having a chain structure but have discrete microgels prepared from different particle of carbopol and entrapment of active content in the
layer and drug release slowly from the external layer. The sieve like external layer is formed surrounding the dosage form and these structure is not soluble in the aqueous media and due to these network formed the active content entrapped in the dosage form and these release with specific rate of release.

When the layer formed outer surface of the dosage form is fully hydrated, the media penetrate inside the dosage form there is pressure built inside the dosage form and due to these there is some breakage in the structure of carbomer and the active content dissolve and comes out form different pieces of hydrogels. Because of these property of the outer layer it behave as sphincter like mechanism in the inner layer the active substance dissolved and the outer layer behave like controlled release layer the active substance penetrate slowly and steadily outside the layer and permits its therapeutic action at specific period of time. Due to these property and structure of carbopbol the solubiloization of active substance and its release profile are dependent on the rates of gel formation and swelling of different carbopbol with its individual mechanism. The swelling and gel forming rate is also dependent on the pH of the in vivo environment. By Increasing the amount of Carbomer the surface area of the polymer will increase and leads to decrease in size of the pore around the external layer and release profile will show the sustained action. All the above mentioned factors will be useful for release mechanism of active content from the dosage form using different grade of the carbopol polymer.

c. Swelling agent / Gel forming polymer

Different grade of Hypromellose

Rational behind the selection

Different grade of Hypromellose powder are hygroscopic in nature after drying even though it is stable in nature. When the hypromellose is available in the solution form it is stable in wide range of pH from 3 to 11. By Increasing the temperature there is change in property of the hypromellose solution it becomes less viscous in nature. When the hypromellose solution cool down it returns to the original state. The gelling temperature of hypromellose is around 50°C to 80°C. The gelling of hypromellose depends on the grade and concentration of the material.
d. Disintegrant

Different grade of Polyplasdone and Povidone.

Rational behind the selection

Different grades of Polyplasdone are used as super disintegrants in the formulation development. When these disintegrants comes in direct contact of media they swell and tends to penetrate more media and finally burst and due to these bursting property the active content comes out from the dosage form and comes in the direct contact of the media and provide its therapeutic action immediately. In the formulation development the povidone solution is used as binder solution.

Advantages of floating dosage form

- These type of dosage form are utilized when the active content is absorbed in the gastric condition or the starting portion of the small intestine. e.g., furosemide.
- The fluctuations in plasma to drug concentration are regulated and the side effected associated with the concentration can be prevented. These property of dosage form is useful when the active content is giving its action in a narrow therapeutic index.
- The pharmacological action of the active content when intended into the formulation by altering or modification in the release rate and buoyancy of the dosage form is not dependent of the site of action.
- Complete release of active substance from the floating dosage form are expected even at the alkaline pH of intestine. The solubilization and penetration of the active content in the gastro intestinal tract and perform its therapeutic action.
- Less absorption of active content from the dosage form is expected if there is low transit time and high intestinal pressure as it occurs in the diarrhea. As in such condition this type of dosage form is used or utilized for the better pharmacological action.

Limitations of floating drug delivery systems

- A sufficient level of gastric fluid is required for the dosage form for floating of the same and release of the active content.
• Active substance which have stability and solubility problems in Gastrointestinal tract are not suitable candidates for these types of systems.

• Drugs that undergo first pass metabolism is less suitable of preparation of the floating dosage form.

• Drugs with irritant property in the Gastrin mucosa are also not suitable for the development of floating dosage form.
1.1.2 Gastro – resistant tablets

The tablets which get released in intestine at basic pH and resist against the acidic pH in the stomach are known as Gastro resistant tablets. These type of dosage form are generally prepared by coating of granules or the tablets i.e gastro resistant coating also known as enteric coated tablets or gastro resistant tablets or delayed release tablets.

Modified dosage form are the dosage form that are prepared to deliver the active content from the dosage form with proposed period of time and predetermine rate and with maximum therapeutic efficacy. So these type of dosage form are better when compare to immediate release tablets. There is much research going on and much progress done on the dosage form with modification in the release rate then also it require much modification in the disorder such as diabetes, heart disease etc. In these type of clinical disorder it required the administration of active content in such a manner that it give effect at the regular time at proper rate and with maximum therapeutic efficacy. The active substance to be administered in such a way that it should be independent of pH when required and which depends on the pH when required. There is need to develop such system which release the active content from the dosage form with modification in the release rate at desired rate of action at desired time.

The modified drug delivery system requires development in the technique for the delivery of protein and peptide. Homeostatis is the mechanism in which human metabolism is maintained via appearance of numerous bioactive peptides.

Sustained release dosage form are the dosage form in which the active content release from the dosage form as per the physiological need by certain mechanism. It is much advantageous that the active content delivered form the dosage form that sensed the signal caused by the disease.

In the human physics there are many segment in the compartment modeling and having the different pH at different segment and on that it depend on the environment stimuli and at physiological state of the human body. So the different active content have different therapeutic activity.
The modification in the dosage form is achieved by addition of polymer having the required property. The utilized polymer have different ionic composition which leads to difference in the density of the polymer and pH of the outer solution. When there is alteration in the pH of the solution it causes swelling or deswelling of the polymer. Active content which entrap in the dosage form, when exposed to the physiologic pH of the solution the polymer swell or deswell and the active content release from the dosage form at desired rate.

Some polymer will ionize and some polymer will not ionize. The ionization of the polymer will resultant from the protonation that depend on the acidic group. When the acidic group will be protonated the polymer will not swell due to its acidic environment. And the vicaversa for the basic group.

There are many different polymer available which swell or release the active content from the dosage form depending on the pH. They are cellulose derivative like cellulose acetate phthalate, hypromellose phthalate, acrylic acid derivative etc. All these polymer have different solubility which depends on the pH of the environment and thus the active content deliver from the dosage form at specific site.

The objective for the preparation of gastro resistance solid oral dosage form are

a) To prevent degradation of acid sensitive drug  
b) To prevent irritation of stomach by certain drugs like sodium salicylate  
c) Delivery of drug into the intestine(site specific)  
d) To repeat its therapeutic action

Active substance like omeprazole, esomeprazole, lansoprasole etc have irritant effect in the gastric environment. Pantoprazole sesquihydrate should be bioavailable in the basic pH of the intestine and unstable in the acidic environment. Some groups of Azoles such as Lansoprazole, Esomeprazole etc. and all grouped azoles are not stable at the acidic environment. For such type of acid labile molecule it is advantageous to prepare the formulation with enteric coat. So the active substance does not come in direct contact of gastric environment and give its therapeutic activity in the basic environment of intestine.
These gastro resistance solid dosage forms are used in the treatment of many conditions such as:\textsuperscript{12}:

- Zollinger-Ellison syndrome
- Gastroesophageal reflux disease
- Dyspepsia
- Barrett’s esophagus
- Peptic ulcer
- Prevention of stress gastritis
- Hyper secretion of acid
- Gastrinomas

The efficacy of gastro resistant tablets have not been searched for each and every case inspite of these condition. There is no change of the length of Burett’s esophagus by the azoles such as proton pump inhibitors.\textsuperscript{13}

In the delayed release dosage form there is release of active content from one or more immediate release is incorporated in to a single dosage form for example repeat action tablets, delayed release tablets, enteric coated pellets filled in capsules, multi unit particulate system i.e. enteric coated particulate compressed to tablets.

**Enteric coatings\textsuperscript{14}**

Delayed release or Enteric coatings are type of coating in which the tables remain intact in the stomach at gastric or acidic environment, but will dissolve and release the contents once it reaches the small intestine at basic environment. Due to enteric coating the active content which are degraded by the acidic environment of the stomach may cause nausea or any other gastric irritation.

Cracking or damage of the film during application or on storage will result in a loss of enteric properties or its desired action. So, consideration must be given to the physical nature of the outer film. Cracking problems might be effectively overcome with the help of proper plasticization. Plasticizer can be used to reduce the permeability of the
polymer films. The choice of suitable Plasticizer is restricted to non water soluble materials or hydrophobic material because these are likely to be most effective.

An proper evaluation is made of solubility specification of species together with an assessment of the intrinsic viscosity of dilute solution of the polymer on the different plasticizers. This determines the maximum interaction between plasticizer and polymer and indicates which Plasticizer is likely to be more effective.

A general rule to follow is to use one part Plasticizer to ten parts polymer.

**Various reason for enteric coating are**  
- Protection of acid labile drug from acidic environment of the stomach
- To protect gastric distress
- Local delivery of the active content in the basic pH of intestine
- Repetation in the pharmacological action
- Protect the active substance from harmful effect of the gastric contents; some of the drugs are prone to be hydrolyzed in acid media e.g. Lansoprazole, Esomeprazole, omeprazole, pantoprazole

**Properties of Ideal enteric coating materials**
- Protection against acidic pH
- permeability
- stability in film property
- Formation of continuous film
- Non toxic
- Cheap
- Ease in availability
- Easy for application
Enteric coating materials

Enteric coatings work because they are insoluble substances they do not dissolve in the acidic environment of the stomach but dissolve in the basic pH of the intestine. Most enteric coatings do not dissolve in solutions with a pH less than 5.5.

Commonly used enteric coatings may be made from:
- Shellac
- Methacrylic acid copolymers
- Acrylic resin
- Cellulose acetate
- Cellulose acetate phthalate
- Hypermellose phthalate
- Hydroxyethyl cellulose phthalate
- Polymethacrylic acid/acrylic acid copolymer
- Polyvinyl acetate phthalate

Earlier enteric coatings use formalized gelatin, this was not reliable because of the polymerization of gelatin could not be accurately controlled. Another was shellac, the disadvantage was polymerization with aging, resulting in poor dissolution of the coating. The most extensively used polymers are Cellulose acetate phthalate, PVAP. The most recently used polymers are Hypermellose phthalate, Methacrylic acid copolymers.

Cellulose Acetate Phthalate (CAP)

It shows effective enteric coating, it only dissolves above pH 6 and may delay drug release longer. Cellulose acetate phthalate is permeable to moisture and gastric fluid in comparison with other enteric polymers and it is susceptible to hydrolytic breakdown on improper storage.

Poly Vinyl Acetate Phthalate (PVAP)

It is less permeable to moisture and simulated gastric juice, it is more stable to hydrolysis on storage. Enteric dosage forms coated with PVAP dissolves at pH 5.
Hydroxy Propyl Methyl Cellulose Phthalate (HPMCP)

It is available in two grades HP 50 and HP 55. HP50 disintegrates at pH5 and HP55 disintegrates at pH5.5. HP 55 solutions are more viscous than HP 50. It has stability similar to that of Poly vinyl acetate phthalate and dissolves in the same pH range. The advantage is that it does not require Plasticizer and more film strength.

Methacrylic acid copolymers

Methacrylic acid copolymers are available in Two grades A and B which differs in the ratio of free carboxyl to ester groups therefore:

Type A has a ratio of 1 : 1 and disintegrates at pH 6. Type B has a ratio of 1 : 2 and disintegrates at pH 7. It is available under the trade names Eudragit L and S correspond to NF types.

Coating equipments

Following are the three equipment used in the coating process

- Conventional coating pan
- Fluid bed energizer
- Coating pan with perforation

Standard coating pan

The conventional coating pan consist very simple system for coating. It included circular coating pan made up of metal mounted on the stand angularly rotates on the horizontal axis by the motor. There is inlet hot air and exhaust system for the circulation of the air. The heating and drying process are controlled by the inlet air. The dosage form meant for coating are kept in the pan and solution or suspension sprayed on to the dosage form with suitable rotation of the pan.
The Fluidized bed coater / Energizer

The Fluid Bed Technology i.e. coating done in fluid bed energizer offers a most efficient coating technique. The major advantage of the Fluid Bed coater is that it is as per Good manufacturing practice standards and it is a closed system. The another advantage of the Fluid Bed energizer is that not only coating but granulation and pellet formation is also possible in the same machine. Fluidized bed coating is a process that takes place inside a fluidized bed equipment whereby a coat is introduced to cover the particular object in order to protect it or modify its behavior. Particulate coating is a type of fluidized bed coating evolving the coating of solid Particles inside the fluid bed coater. In this process a layer is formed onto the surface of fluidized solid by spraying with a suspension or solution of the coating material. Fluidizing gas is used to dry the deposited solution to form a coat on the surface of the particle and to make the particle dry and smooth.

There are different method of using fluidized bed technology. For e.g. liquids can be sprayed to fluidized particles in a variety of ways, including top, tangential and bottom. For a given product, each specified method can show remarkably different finished product characteristics.

Fluidized beds for film coating can be divided into three groups:

- Top spray
- Tangential spray
- Bottom spray

Bottom spray coating

Material passing through coating partition receives a layer of coating material, dries in the expansion chamber, and falls back in a semi fluidized state. Material circulates rapidly in this fashion and receives layer of coating material, dries in the expansion chamber, and falls back in a semi fluidized state material circulates rapidly in this fashion and receives a layer of coating on each pass through the coating partition. This design allows the substrate particles to be pneumatically transported upward through the coating partition and downward outside this partition. The ring of large
holes on the periphery of perforated plate prevents the accumulation of material at the wall. It has been used for coating pellets, small particles and tablets.

**Fluid bed coating**

Particles smaller than approximately two mm should be coated in fluid bed energizer, because with decreasing particle diameter the specific surface area of a particle increase. In order to achieve acceptable process times, the high efficiency of fluid bed compared to pan coating equipment shows clear advantages in particles coating processes. The required coating weight gain is much higher than tablet coating processes.

**Shape**

To achieve good flow properties, while needle shaped particles show poor flow properties and tend to form lumps, spherical particles with smooth surfaces are preferred. Other advantage of the latter is the increased risk of breakage during the coating process, creating uncoated spaces and leading to an increased coating weight gain. Besides pellets and crystals, granules can also be used as substrates as a disadvantages we may have uneven surfaces and often increased abrasion compared to the shapes mentioned first, which can also lead to increase in the surface areas which requires higher amounts of coating.

**Size**

Usual particle sizes are in a range of 0.2 mm to 1.2 mm. Smaller particles may have problematic flow properties in higher scale and may tend to break if the length to diameter ratio is two. In order to avoid cleavage by chewing, the coated particles should have a size of 0.4 mm smaller end products may given a better mouth feeling but increasing specific surface areas requires higher coating amounts.

Smaller particle size are required if particles are administered from sachets or incorporated into chewable tablets.
Top / Tangential / Bottom Spray

The top spray is used for granulation process and particle coating. Compared to other fluid bed coating technologies, the top spray method is susceptible to form porous film structure, especially if organic coating solution are processed. Bottom spraying is the traditional method in particle coating. Due to a more uniform particle movement, better film properties can be achieved when compared to the top spray method, and the required polymer weight gain for a certain function is much lower. A disadvantage is that in case of nozzle blockage during the coating process, the product must be discharged before the nozzles can be cleaned. Tangential spraying system is commonly fitted with a rotating bottom plate. It achieve film qualities nearly as good as bottom spraying technique. The rotation of the plate nicely supports product movement, so that the required air amount is mainly used for drying process and only to a smaller degree for the product movement.

Nozzles for the particle coating

Spray gun are air borne with a round spray pattern. Some equipment or air channel is fitted with a double air supply which is used for common atomizing air, which surrounds the spray pattern, preventing over wetting of the product, reduces agglomeration and reducing spray drying effects.

Pump system

Peristaltic pumps is fitted with silicon tubing. Silicon tubing can be selected in a wide range with difference in internal diameters in order to keep the varying flow speed and hence to prevent sedimentation. Therefore the use of silicon tubing with small internal diameters are more preferable. Alternative pump systems include piston pumps and gear pumps.\textsuperscript{14,15}

Rotating disk granulation

This is recent and advance granulation technique which utilize centrifugal drive. The basic design shows a rotating disk in the product container. These techniques have
been extended to coating operations of pellets, granules, particles and when join with external chamber to create these equipment.

Simultaneously disk rotates with varying speeds and moves the product by the force produced by the centrifugation from the external portion and lifted by air stream. As the granules inside the disc will be move upward because of the negative pressure and the same process will be repeated throughout the process. The fluidization pattern is often described as spiraling helix.

**Pelletization**

**Pellets**\(^\text{16}\): Pellets can be defined as small, semi spherical or spherical solid particles, ranges between 500 micron to 1500 micron and prepared mainly for orally administrated active content, prepared by the agglomerates of powders of active content and in active excipients using suitable process.

- For the preparation of the pellets it should contain maximum concentration of active substance and functional excipient to prepare the dosage form within the specific limit. They should be smooth surface and near spherical, which are mandatory for seal coating or subsequent coating.

- The pellets produced by any method should have smooth surface and spherical surface which is required for further coating of the pellets.

- The size of the sphere should be as narrow as possible to overcome the problem of insufficient coating and for consistency in the coating. Different size of pellets are available for coating. (between 600 micron to 1000 micron)

**Significance of pellets**

Pellets may have different applications in different industries.

It just requires an innovative bend to use it at consitant level and to derive maximum profitability. The the uniform size of the pellets, its nature its surface area, nature of the surface all these will be in use for good coating characteristics for each particle to keep the less variability between particles and different production batches.
Highlighted below are some of the few example where smooth surfaced uniform pellets are being successfully used:

- Aesthetic appearance of the products.
- Coating of pellets can be done with different drugs to provide a modified release rate.
- Varied applications are possible in the pellet form. Eg: controlled release.
- In case for immediate Release Products larger surface area of pellets provide better distribution of active substance without variation in the content.
- Incompatible products can be formulated into pellets & delivered in a single dose by encapsulating.
- It is used to avoid dusting of powder.
- The thickness of the layer on the pellets dictates the rate at which the active contents are released from the coated particles.
- The coating material can be colored with a dye material to differentiate in the coating so that the beads of different coating thickness will be darker in color and distinguishable from those having less coats.
- The beads of different thickness of coatings are blended in the desired proportions to give the desired pharmacological effect.
- By selecting the proper formulation, ingredient, process, parameters, processing conditions and processing equipment it is possible to attain uniform, smooth surfaces pellets.

**The most common advantages of pelletization are**\(^\text{17}\)

- Less susceptible to dose dumping.
- Improved appearance of the product.
- Provide safety and efficacy
- Provide flexibility in formulation development.
• Reduction in variation in therapeutic effect
• Disperse freely
• Improve gastric absorption of drug and also reduce the concentration maximum.
• No issue in the flow property

**Theory of pellet formation**

There are different mechanism and different theories for the formation of the pellets. For the understanding of pellet formation or granulation it is advantageous to know the types, mechanism, concept theory in details. There are different equipment, different excipient with numerous property and its pharmacological action should be understood in detail. There are different equipment like GPCG glatt, fluid bed processor, extrusion and spheronization, fluid bed energizer etc. The basic formation of pellets divided in to the three different region

• Nucleation
• Transition
• Ball growth

**Methods of preparing pellets**

Drug layering via suspension or solution, powder layering technique, compaction of active component are generally used in formulation development of pellets. There are some modified technique like melt extrusion which can be prepared using high shear mixer.

**Powder layering**

Powder layering is a technique that allows the layering of dry powder of drugs or excipient on the core with the help of binder solution or suspension. In the powder layering technique it utilize dry powder as well as binding agent so it required
equipment like spheronizer at the earlier stage. The liquid solution sprayed on the powder from one side and from the other side it spray solid particulate and hence it binds to the granules and make a layer over the granules.

**Pelletization by extrusion and spheronization**¹⁹

These process involves first making of the extrudes using processing equipment like extrusion from the powder material/fines and then converting the extrudes into beads using the equipment called spheronizer. The powder material could be any kind of powder such as fine powder of active substance, drug powder, detergent powder, Ayurvedic powder, food ingredient powder, nuclear powder etc.

**Other pelletization methods**

Inspite of above mentioned technique there are also other pelletization technique such as balling, globulation, compression, cryopelletization. These technique are used for preparation of the pellets but due to its unavailability, lack of interest, traditional attitude these are not utilized with ease.

Globulation or droplet formation consists two different related mechanism they are

1) Spray drying
2) Spray congealing

**Spray drying**

Spray drying is the simple process in which an active content is sprayed with in active excipient or without in active excipient on the sugar sphere of microcrystalline cellulose in the specified condition after optimization. These technique is widely utilized for regulation in the dissolution profile and so increase in the bioavailabilty of less soluble active content.
Spray congealing

It is the method in which the active substance is melted, dissolved in media, disperse in media in hot melt of fatty acid structure and it is then taken into the process chamber where the product temperature is kept less when compare to the temperature of melting point of different formulation component. Because of these property the spray congealing technique is capable of modified release rate of formulation with immediate or sustained effect.

Compression

It is one of the most common technique for the formation of the pellets. Prepare pellets of specified sizes and varying shapes by applying pressure on to the dry powder or blend. There is not much difference in the chemical and physical attributes of tablets manufacturing process and the spherecical particle formed be these process.

Cryopelletization

Cryopelletization is a process in which the liquid formulation is converted in to solid spherical particles, granules or pellets in the presence of liquid nitrogen as medium. The shape depends up on the distance of the droplet travel before contacting liquid nitrogen.

Balling

It is also most common and ancient method for the preparation of the spherical particles of different size. It can be prepared by rolling or tumbling. The rolling of tumbling motion can be achieved by using different equipment like drums, pan, spheronozation, processor etc.
1.2 Drug profile

1.2.1 Introduction of Metformin hydrochloride

Metformin hydrochloride is a biguanide derivative in a class of oral hypoglycaemic agents. It exerts glucose lowering effect and used in the treatment of diabetes mellitus. Metformin hydrochloride is well absorbed in the gastrointestinal tract.

1.2.1.1 Physicochemical Properties: -

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>Metformin Hydrochloride</td>
</tr>
<tr>
<td>Synonym</td>
<td>Metformini Hydrochloridum</td>
</tr>
<tr>
<td>Chemical Name</td>
<td>1, 1- dimethyl biguanide hydrochloride</td>
</tr>
<tr>
<td>Chemical formula</td>
<td>C₄H₁₁N₅ HCl</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>165.62</td>
</tr>
<tr>
<td>pKa</td>
<td>11</td>
</tr>
<tr>
<td>Melting point</td>
<td>222 degree C to 226 degree C</td>
</tr>
<tr>
<td>Partition Coefficient</td>
<td>2.6</td>
</tr>
<tr>
<td>pH of 1% aqueous solution</td>
<td>6.68</td>
</tr>
<tr>
<td>Dose</td>
<td>500 mg to 3000 mg in divided dose</td>
</tr>
<tr>
<td>Category</td>
<td>Hypoglycemic</td>
</tr>
<tr>
<td>Organoleptic character</td>
<td>White, hygroscopic crystalline powder</td>
</tr>
<tr>
<td>Solubility</td>
<td>Slightly soluble in SDS ethanol (95 %), practically insoluble in acetone, dichloromethane, ether, chloroform and completely soluble in purified water.</td>
</tr>
</tbody>
</table>
\( \lambda_{\text{max}} \): 233 nm in pH 6.8 phosphate buffer

**Heavy metals:** NMT 20 ppm

**Sulfated ash:** NMT 0.1 % w/w

**Half-life:** 2 hrs. – 6 hrs. after oral administration

**Heavy metals:** Not more than 20 ppm

**LOD (loss on drying):** NMT 0.5 % w/w, determined on one gm by drying in an oven at 105°C.

**Particle size:** 100 % particle pass through 100 mesh ASTM.

**Storage Condition:** Store at 20 degree C to 25 degree C

**Standards:** Metformin Hydrochloride contains NLT 98.5 percent and NMT 101.0 percent of Metformin Hydrochloride. Calculation done on the basis of dried substance.

**Assay:** Weigh about 60 mg, dissolve in 4 ml of anhydrous formic acid, transfer 50 milliliter of acetic anhydride and carry out non aqueous titration, end point is determined by potentiometrically. First perform the blank determination and simultaneously make any correction. Each 0.008281 gram of Metformin Hydrochloride is equivalent to 0.1 molar perchloric acid.

**Dosage form of Metformin Hydrochloride**

**Metformin Hydrochloride tablets**

**Usual strengths:** 500 mg/ 850 mg and 1000 mg

**Standards:** It contains NLT 95.0 percent and NMT 105.0 percent of the stated amount of metformin hydrochloride, \( C_{4}H_{11}N_{5} \), HCl.

**Analysis:**

Chemical formula of Metformin Hydrochloride is 1,1-dimethyl buguanide Hydrochloride and is official in official in IP \textsuperscript{21} and BP \textsuperscript{22}. The analysis of Metformin Hydrochloride can be done by various method and by various equipment such as High performance liquid chromatography, ultra violet spectophotometry etc. Few Spectrophotometric\textsuperscript{20}, gas chromatographic \textsuperscript{23} and HPLC \textsuperscript{24,25,26,27} methods have been reported for its estimation in its dosage form. Metformine Hydrochloride can be detected in body fluids and blood plasma by sophisticated methods.\textsuperscript{28,29,30}
1.2.1.2 Pharmacology

Pharmacokinetics and bioavailability\(^{31,32}\)

- **Absorption:**
  The Metformin Hydrochloride when given orally in the fasting condition the bioavailability is around 50 percent to 60 percent. Varying in the concentration of the active content i.e. Metformin Hydrochloride from 500 mg to 2550 mg it does not show dose proportionality with increase in the active content. These might be due to decrease in the absorption of metformin hydrochloride throughout GIT. It is not due to change in the elimination of the active component. There is food effect on the Metformin Hydrochloride when administered orally. When active content is administered with specific meal it shows approxly forty percentage decrease in maximum concentration and twenty five percentage less area under curve of peak plasma concentration. There is no significant clinical property known and it had no mean. When a unit dose of metformin hydrochloride is given the maximum concentration is achieved around seven hours within a range of three to seven hours. Maximum concentration is decreased to about twenty percentage and area under curve remains similar for metformin hydrochloride. When the dosage form of Metformin Hydrochloride given with food the area under curve increases about 50 percent. There is no effect of food on maximum concentration and time at which maximum concentration is achieved when the Metform Hydrochloride is administered orally. When the food taken with high and low fat it give same effect on the various pharmacokinetic parameters.

- **Distribution:**
  Sulfonl ureas bound more than 90 % to plasma proteins while Metformin hydrochloride bound to plasma proteins comparatively less. Metformin hydrochloride penetrate in to erythrocytes. When given with mentioned doses the blood concentration of metformin hydrochloride reaches in twenty four to forty eight hours and concentration is less than one µg per ml. When clinical trial
performed of metformin hydrochloride the plasma concentration does not exceed five µg per ml even at higher dose.

- **Metabolism and Elimination:**
  - It does not undergo any hepatic metabolism.
  - Creatinine clearance is comparatively lower than renal clearance.
  - Almost 90 percentage of active content is eliminated via renal.
  - Half life of Metformin hydrochloride is around six hours in plasma at elimination stage.
  - Elimination half of Metformin Hydrochloride is around seventeen hours in the blood.

**Mechanism of action**
Metformin hydrochloride improves the insulin sensitivity, decrease the hepatic glucose production, decrease in the intestinal absorption of the glucose. Metformin hydrochloride does not cause hyperinsulinemia. Metformin hydrochloride when taken orally improves the glucose tolerance in subject with type 2 diabetes. It lowers the post prandial plasma glucose. Metformin Hydrochloride does not produce hypoglycemia. When the human being is under the treatment of Metformin Hydrochloride plasma insulin response may change but there might not any change in the insulin secretion.

**Adverse effects**
There are some common side effect associated with Metformin Hydrochloride:
- Gas
- Nausea
- Bloating
- Vomiting
- Loss of appetite
- Diarrhea
- Lactic acidosis
1.2.1.3 Dosing information

**Adults:** The initial dose of metformin hydrochloride for adults is five hundred mg for two times in a day and for eight hundred and fifty mg to be taken for one time in a day. The dose of Metformin Hydrochloride is increased to two thousand mg per day.

**Pediatrics:** Metformin Hydrochloride when given to children it is given as 500 mg twice per day, 850 mg once per day and given with meal. The dose to be increase in the increment of 500 mg per week to maximum of 2000 mg per day and that to be given in the divided doses.

1.2.1.4 Drug interaction

**Glyburide:** When glyburide is given with metformin hydrochloride there is decrease in level of maximum concentration and area under curve but maximum variation observed. Due to the administration of single dose to the patient the correlation between metformin hydrochloride and the glyburide in the plasma is not established and the level of glyburide in plasma have no any clinical significance.

**Furosemide:** Pharmacokinetic parameters of both compounds i.e. metformin and furosemide were studied and their effect had been established. There is increase in plasma concentration of metformin hydrochloride in the plasma and blood by 22 % and area under curve increase by 15 %, and there is no change in the renal clearance of Metformin hydrochloride. There is no further studies done or information available when metformin hydrochloride and furosemide administered simultaneously.

**Cationic drugs:** The example of these drugs are vancomycin, trimethoprim, triemterine, ranitidine, quinine, amiloride, digoxine, morphine, procainamide, quinidine. These cationic drug when comes in contact with metformin they chemically interact and are eliminated by the tubular secretion.

**Drugs food interaction:** When metformin hydrochloride is taken with meal the extent of absorption decrease and there is delay of pharmacological effect. The 850 mg metformin hydrochloride when administered orally with meal there is decrease in around 40 % of the plasma concentration of the blood of metformin and decrease in the AUC by 25 % in half an hour. When the metformin hydrochloride administered under fasting condition there is increase in the peak plasma concentration and extent of absorption also increase.
1.2.1.5 Contraindications

Contraindications are shown in Table 1.1

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nausea</td>
</tr>
<tr>
<td>2</td>
<td>Previous history with lactic acidosis</td>
</tr>
<tr>
<td>3</td>
<td>Use of intravenous radio contrast</td>
</tr>
<tr>
<td>4</td>
<td>Gastrointestinal disorder</td>
</tr>
<tr>
<td>5</td>
<td>High alcohol intake</td>
</tr>
<tr>
<td>6</td>
<td>Renal disease</td>
</tr>
<tr>
<td>7</td>
<td>Hepatic disease</td>
</tr>
<tr>
<td>8</td>
<td>Any condition predisposing to tissue hypoxia</td>
</tr>
<tr>
<td>9</td>
<td>History of allergic reaction to metformin</td>
</tr>
<tr>
<td>10</td>
<td>Hepatic disease</td>
</tr>
<tr>
<td>11</td>
<td>Vomitting</td>
</tr>
<tr>
<td>12</td>
<td>Acute or severe cardiac or respiratory dysfunction</td>
</tr>
<tr>
<td>13</td>
<td>High alcohol intake</td>
</tr>
<tr>
<td>14</td>
<td>Severely ill or unstable hospitalized patients</td>
</tr>
<tr>
<td>15</td>
<td>Patient to undergo surgery</td>
</tr>
</tbody>
</table>
1.2.2 Introduction to Glimepiride

Glimepiride is utilized for the pharmacological effect against type two diabetes mellitus. It is used in the treatment when activities like low calorie meal, physical exercise etc are not useful.

1.2.2.1 Physicochemical Properties\textsuperscript{35,36}

Glimepiride is fermentation product of Aspergillus terreus.

Glimepiride is synthetically derived by fermentation.

Glimepiride is hypoglycemic agent.

**Empirical formula:** $C_{24}H_{34}N_4O_5S$

**Chemical name:** urea derivative of 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl]phenyl]sulphonyl]-3-(trans-4-methyl cyclo-hexyl) urea.

**Molecular weight:** 418.57

![Figure 5: Structural formula.](image)

**Description:** Glimeperide is white to off white, odourless, crystalline powder.

**Solubility:** Glimepiride is practically insoluble in water, very soluble in chloroform and soluble in dimethyl formamide.
Partition Coefficient: 1.8

Polymorphism: It does not show any polymorphism.

Melting Point: 207°C

Crystal Properties & Isomerism: Glimepiride does not exhibit isomerism.

Glimepiride is an alkaline active substance with short half life of six hours to eight hours, exhibits very low water solubility (< 0.004 mg/ml) and bioavailability of 100%.

1.2.2.2 Pharmacokinetics

• Absorption:
  When Glimepiride is orally administered it gets totally absorbed from the gastrointestinal tract. There are also reported studies of Glimepiride when given in single dose to normal subject and multiple doses to the patient with Non insulin dependent diabetes Mellitus. The significant pharmacological effect have been observed within one hour after the oral administration and maximum concentration is achieved within two to three hours. When the Glimepiride had been given with food there in increase in the rate of maximum concentration to 12 % i.e. increase in tmax and the maximum concentration and area under curve reduced to about 8 % and 9 % respectively.

• Distribution:
  After dosing of Glimepiride in normal subject the volume of distribution were 8.8 liter and the total body clearance was 47.8 mL/minute. Protein binding of Glimepiride was found to be greater than 99.5 %.

• Metabolism:
  There is complete metabolism of Glimepiride by the oxidative biotransformation when given the Glimepiride through intravenous route or through oral dose. The active metabolite of Glimepiride are cyclohexylhydroxy methyl derivative and carboxyl derivative.
• **Excretion:**

When the Glimepiride is given intravenously there is no biliary excretion of Glimepiride or its metabolite (M1) has been observed.

When the Glimepiride is given orally approximately sixty percent of the total radioactivity was recovered in the urine in seven days. Its metabolite M1 and M2 were recovered up to eighty percent and ninety percent respectively in the urine. Approximately around forty percent of the total radioactivity were recovered in the faces.

**1.2.2.3 Pharmacodynamics**

**Mechanism of action of Glimepiride**

Glimepiride lowers the glucose level in the blood and the plasma.

Glimepiride increases the release of insulin from the pancreatic beta cells.

Glimepiride plays an important role in the pharmacological activity of sulfonylureas.

**Indication of Glimepiride**

Glimepiride is given in the treatment of type two diabetes mellitus.

Glimepiride is given when physical exercise, weight reduction, low calorie diet are not adequate.

**1.2.2.4 Dosage and Administration:**

The maximum recommended dose is 6 mg Glimepiride per day.

The optimum recommended dose of Glimepiride is one mg per day to six mg per day.
1.2.3 Introduction to Omeprazole

Omeprazole is benzimidazoline derivative, acid labile, proton pump inhibitor.

1.2.3.1 Physicochemical Properties

Omeprazole

![Structural formula](image)

**Figure 6**: Structural formula.

**Empirical formula**: $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$

**Molecular weight**: 345.42

Omeprazole is a white or almost white powder. Omeprazole is very slightly soluble in water, soluble in methylene chloride, sparingly soluble in ethanol (96 percent) and in methanol. It dissolves in dilute solutions of alkali hydroxides.

**Polymorphism**: It shows polymorphism.

**Chemical name**: 1H-Benzimidazole, 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphynyl]benzimidazole.

**Description**: White of almost white powder.

**Solubility**: Soluble in methylene chloride, very slightly soluble in water, sparingly soluble in ethanol, and dissolve in dilute solution of alkali hydroxide.

**Melting Point**: $154^\circ\text{C}$.
1.2.3.2 Pharmacokinetics

- **Absorption and distribution**
  Omeprazole is not stable in the acidic media of stomach and meant for oral administration so to protect the omeprazole from acidic media enteric coating is required.
  Omeprazole is completely absorbed in the alkaline pH of the small intestine.
  Absorption of omeprazole takes place from three hrs. to six hrs. The bioavailability of acid labile drug i.e. omeprazole is approximately 35%. But when the omeprazole is given daily the systemic bioavailability increases to 60%. There is no much difference in the apparent volume of the distribution in healthy human being and the patient which is approximately 0.3 L/kg. In the patient with old age with hepatic insufficiency the volume is slightly reduced. Omeprazole is 95% bound to plasma protein.

- **Metabolism and excretion:**
  When the omeprazole is administered orally the elimination half life of omeprazole is comparatively less and it is less than one hour and if the treatment is longer period of time still there is no any change in the elimination half life of omeprazole.
  Azoles derivative like omeprazole metabolized by cytochrome P450 in the liver.
  There is hydroxyl omeprazole formed which is major metabolite and is polymorphically classified.
  Almost more than eighty percent of omeprazole is excreted in urine when given orally and the remaining quantity of omeprazole excreted in the faeces which originated from the bile secretion. There is no any pharmacological effect of metabolite on the gastric acid secretion.

1.2.3.3 Pharmacodynamics

- **Actions:**
  Omeprazole is acting rapidly and provide its pharmacological activity by reversible inhibition of gastric acid secretion. Omeprazole inhibits acid pump in the periatel cell.
It is racemic mixture of two active isomers which regulates secretion of gastric acid by specifically targeted mechanism of action.

- **Mechanism of action:**

  Omeprazole is pharmacologically active when comes in contact with acidic environment of stomach. Omeprazole is base and inhibits H+K+ATPase. Omeprazole binds to the enzyme at later stage of gastric acid formation and so omeprazole enable the development of gastric acid.

  The pharmacodynamic effect of the omeprazole can be explain on the basis of mechanism of the gastric acid secretion.

**1.2.3.4 Pharmacopoeial Status:**

  Omeprazole drug substance is official in Ph. Eur.\textsuperscript{42} and USP\textsuperscript{43}, and Omeprazole delayed-release capsules are official in BP and USP.
1.2.4 Introduction to Doxycycline hydrochloride

Doxycycline is available as monohydrate or as hydrochloride hemiethanolate also called as the hyclate. Doxycycline hydrochloride is a broad-spectrum antibiotic.

1.2.4.1 Physicochemical Properties

Generic Name: Doxycycline Hydrochloride

Chemical Name: 1, 1- dimethyl biguanide hydrochloride.

The structural formula for doxycycline hydrochloride is:

![Chemical Structure](image)

Chemical formula: \( C_{22}H_{24}N_{2}O_{8} \cdot HCl \)

Molecular weight: 512.9

Melting point: 201°C

Dose: 50 mg /100 mg

Description: A yellow hygroscopic crystalline powder.

Solubility: It is practically insoluble in chloroform, ether; doxycycline is soluble in solution of alkali hydroxide and carbonates at basic pH. It is soluble in purified water and slightly soluble in alcohol.
1.2.4.2 Pharmacology

- **Mechanism of Action**

Doxycycline has different and wide pharmacological activities like it is antimicrobial, bacteriostatic, it is broad spectrum antibiotic. For the different pharmacological activity there is different mechanism of action for doxycycline hydrochloride. For antimicrobial activity it inhibits protein synthesis. Due to the active substance there is no binding of m RNA to t RNA. And this binding is much sensitive. Because of such mechanism of Doxycycline it prevents the growth of organism.

1.2.4.3 Pharmacokinetics

- **Absorption**

There is no effect of food on absorption and to achieve peak concentration of Doxycycline hydrochloride. It exerts similar effect when ingested with or without food or milk.

- **Distribution**

Doxycycline hydrochloride distributes in most of the body tissues, plasma, serum, cavities, fluids. Maximum concentration of doxycycline is achieved at two hours when 200 mg dose administered orally.

The apparent volume of distribution of doxycycline is around 0.7 L per kg.

There is variation in plasma protein binding of doxycycline hydrochloride.

- **Elimination**

Doxycycline hydrochloride is eliminated through urine as unchanged form. It is excreted in high concentration. The serum half life of doxycycline are around 18 hrs to 22 hrs. The elimination of doxycycline does not have any effect when there is age, hepatic or renal failure, haemodialysis.
1.3 References


31) Physician Desk Reference, (Glucophage), 1079.


