Chapter – 1

INTRODUCTION
1.1. DRUG DELIVERY SYSTEMS:

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of drug release. Drug delivery system may be a formulation of the drug to administer it for a therapeutic purpose or a device used to deliver the drug \(^1\). The science of drug delivery may be described as the application of chemical and biological principles to control the in vivo temporal and spatial location of drug molecules for clinical benefit \(^2\). The drug delivery systems are based on interdisciplinary approaches that combine polymer science, pharmaceutical science, bio-conjugate chemistry, molecular biology. New drug delivery applications are largely based on promoting the therapeutic efficiency of the drug molecule and minimizing its toxic effect by increasing the amount and persistence of a drug near the target cells and reducing the drug exposure to non-target cells \(^3\).

In the form of a DDS, an existing drug molecule can get a new life, thereby increasing its market value and competitiveness and extending patent life. Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety, and improved patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery systems \(^4\).

1.1.1. Characteristics of Ideal Drug Delivery Systems \(^3\): Characteristics of an ideal drug delivery system are as follows:

- It should increase the bioavailability of the drug.
- It should provide for controlled drug delivery.
• It should transport the drug intact to the site of action while avoiding the non-
diseased host tissues.
• The product should be stable and delivery should be maintained under various
physiological variables.
• The same method should be applicable to a wide range of drugs.
• It should be easy to administer to the patients.
• It should be safe, reliable and cost-effective.

1.2. ORAL DRUG DELIVERY SYSTEMS:

Oral administration is the most convenient and preferred means of any drug
delivery to the systematic circulation. Oral dosage forms have made its progressive
journey through conventional release to delayed release to sustained release and site-
specific delivery as well. The design of oral drug delivery systems should be primarily
aimed to achieve more predictable and improved bioavailability. The primary objective
of oral controlled release drug delivery system is to ensure safety of drugs as well as
patient compliance. This is achieved by better control of plasma drug levels with less
frequent self-administered dosing yielding constant availability of the drug at the site of
absorption.

1.2.1. Issues, Challenges and opportunities in Oral Drug Delivery: Historically, oral
route being preferred for administration of drugs for systemic as well as local effect due
to ease of administration and widespread acceptance by the patients. Conventional oral
dosage forms such as conventional tablets, capsules, oral liquids carry the drug
substances to GIT without offering any control over the rate and extend of drug delivery
at the site of absorption. This type of non-specific drug delivery systems cause great
fluctuations in plasma drug levels which may lead to therapeutic ineffectiveness of the
administered drug or may produce undesirable toxicity and side effects. Moreover, this most popular route concerns over certain limitations those includes variation in the systemic availability, degradation of drug molecules in acidic and enzyme rich environment, poor perfusion rate of gastric lumen, fast-pass metabolism, non-specific distribution of drug in the body \(^{(1)}\).

In spite of its several limitations, this route offers several opportunities for pharmaceutical researchers for delivery of drugs for systemic action. Oral route offers non-invasive and painless administration of pharmaceutical substances. Moreover it is safer and economic route for administration of variety of dosage forms those includes solid, liquids and semisolid formulations. Modulation in release behavior and fabrication of novel drug delivery system provide broader prospect of oral route of drug delivery \(^{(3, 4, 5)}\).

1.2.2. Novel Approaches to improve bioavailability of drug: Majority of the orally administered drugs are well absorbed from all the regions of the GIT, while some are absorbed only from specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as due to the degradation of the drug by microorganisms present in the colon. Systemic availability of orally administered drugs always raised difficulties for formulators and researchers. Many diverse approaches have been embraced to overcome this issue. Intense efforts being paid by scientists and researcher in this respect, which brings about the newer strategies and concepts in this regard. Following is the brief summary of successful approaches to improve bioavailability of orally administered drug (Figure 1.1):
Figure – 1.1: Flow-chart diagram depicting formulation based approaches to improve bioavailability of drugs.

In instances, where a drug has a clear cut “absorption window,” i.e., the drug is absorbed only from specific regions of the stomach or upper parts of the small intestine it may not be completely absorbed when administered in the form of a typical oral sustained release or controlled release drug delivery systems. This is due to the relatively short gastric emptying time in humans, which normally averages 2-3 hours through the major absorption zone. It may cause incomplete drug release from the dosage form at absorption sites leading to reduced efficacy of the administered dose. It is apparent that for a drug having such an “absorption window,” an effective oral DDS should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a longer period of time. For such type of drugs, increased or more predictable bioavailability would result if controlled release systems could be
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retained in the stomach for extended periods of time. This type of drug delivery systems popularly known as Gastro-retentive Drug Delivery Systems (GRDDS).

1.3. GASTRO RETENTIVE DRUG DELIVERY SYSTEMS (GRDDS): Localization of a drug delivery system in a specific region of the Gastro-Intestinal Tract (GIT) offers numerous advantages, especially for drugs having narrow absorption window. Gastro-retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper GIT for local or systemic effects. Gastro-retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs\(^\text{(6, 7, 8)}\).

A number of gastro-retentive drug delivery approaches has been designed and developed those includes high density systems that can retain in the bottom of the stomach\(^\text{(9)}\), low density systems that floats in gastric fluid\(^\text{(10)}\), mucoadhesive systems that adheres to the gastric mucosa\(^\text{(11)}\), extendible, unfoldable, or swellable hydrogel systems\(^\text{(12)}\), super-porous hydrogel systems\(^\text{(13)}\), magnetic drug delivery systems\(^\text{(14)}\) etc.

1.3.1. Need for Gastro-retentive Drug Delivery Systems: Prolonged gastric retention improves bioavailability by increasing the duration of drug release, reducing drug waste, and improving the drug solubility that are less soluble in a low pH environment\(^\text{(15)}\). Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc. Gastro-retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index\(^\text{(16)}\).
1.3.2. Factors affecting Gastro Retentions:

- **Density**: Gastric retention time (GRT) depends on the density of dosage form. Density of DDS also affects the gastric emptying rate and location of the system within the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus.

- **Size and shape of DDS**: Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention.

- **Fed or unfed state**: Under fasting conditions, GI motility is characterized by periodic strong motor activity or the Migrating Myoelectric Complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

- **Nature of meal**: Feeding of indigestible fibrous food, fatty food, protein rich diet can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging GRT.

- **Frequency of feed**: The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.
• Other factors such as age, gender, posture, concomitant administration of other drugs, disease state etc. can alter the GRT of DDS.

1.3.3. **Innovative approaches in Gastro-Retentive Drug Delivery Systems:** Last two decades witnessed many novel innovative approaches. These approaches successfully demonstrated improved GRT for drugs (Figure 1.2 & 1.3). These approaches are based on physical, chemical and biochemical understanding of drug delivery systems and physiological basis of gastrointestinal tract. Various approaches for gastro-retentive drug delivery system are summarized below:

![Gastro-retentive Drug Delivery Systems](image)

**Figure – 1.2:** Flow-chart diagram depicting Novel Approaches for Gastro-Retentive Drug Delivery Systems

1.3.3.1. **High Density (Sinking) System:** This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~1.004 gm/cm³). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and...
titanium oxide etc.\(^{(17)}\). The materials increase density by up to 1.5 - 2.4 gm/cm\(^3\). A density close to 2.5 gm/cm\(^3\) seems necessary for significant prolongation of gastric residence time \(^{(18)}\). But, effectiveness of this system in human beings was not observed\(^{(19)}\).

1.3.3.2. **Floating drug delivery system:** Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability \(^{(20)}\). This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine \(^{(21)}\). These types of system have a bulk density less than gastric fluids and so 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. This type of drug delivery system is based on two different mechanisms for its buoyancy, namely non-effervescent and effervescent system.

1.3.3.2.1. **Effervescent (Gas generating) system:** Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers and effervescent components. In this system carbon dioxide is released and causes the formulation to float in the stomach \(^{(22)}\).

1.3.3.2.2. **Non-effervescent system:** Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment \(^{(23)}\). Microballoons / hollow microspheres loaded with drugs to prolong the gastric retention time of the dosage form. The microballoons floated
continuously over the surface of gastric content. Hollow microspheres are considered to be one of the promising buoyant systems because they combine the advantages of multiple-unit system and good floating\(^{(24)}\).

1.3.3.2.3. **Micro-porous gel system**: This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with undissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption\(^{(25)}\).

1.3.3.3. **Swelling and Expanding System**: These are the dosage forms, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained for a longer period of time. These systems may be named as “plug type systems”, since they exhibit the tendency to remain lodged at the pyloric sphincter. On coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical/chemical cross-links in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and hence maintain the physical integrity of the dosage form\(^{(17)}\).

1.3.3.4. **Mucoadhesive Systems**: Mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucous membrane and serve as the potential means of extending the GRT of DDS in the stomach through increased the intimacy and duration of contact of drug delivery device with the mucosal membrane. In the later section in this chapter, a comprehensive discussion on mucoadhesive drug delivery is presented.
1.4. MUCOADHESIVE DRUG DELIVERY SYSTEM:

Oral Controlled Release Mucoadhesive Drug Delivery System (MDDS) is one of the most promising DDS to prolong the gastric residence time at the site of absorption. Professor Joseph R. Robinson, also known as “Father of Mucoadhesive Drug Delivery Systems” at the University of Wisconsin pioneered the concept of mucoadhesion as a new strategy to prolong the residence time of various drugs on the mucosal surfaces (26).

Bioadhesion can be defined as “the state in which two materials, at least one of which is biological in nature, are maintained together for a prolonged time period by means of interfacial forces” (27). Mucoadhesion is defined as the phenomenon of a material (synthetic or natural) to adhere to the mucosal layer (28). These surfaces are held together by interfacial forces for an extended period of time. Mucoadhesion is the ability of materials to adhere reversibly to mucosal surfaces in the human body and provide a temporary retention. This property of certain polymeric materials has been widely used to develop dosage forms for buccal, oral, nasal, ocular and vaginal drug delivery.
1.4.1. The Mucous Membrane and Mucin: Mucosal membranes of human organism are relatively permeable and allow fast drug absorption. They are characterized by an epithelial layer whose surface is covered by mucus. The epithelial cells of the mucosal tissues are coated with slippery viscous mucous. The mucus contains glycoproteins, lipids, inorganic salts and 95% water by mass, making it a highly hydrated system. The main functions of mucus are protecting and lubricating the epithelium and other additional functions depending on the epithelium covered. Mucus thickness can vary from 50-450 μm in the stomach to less than 1 μm in the oral cavity \(^{(27)}\). The mucous site most used for drug administration and absorption is gastrointestinal \(^{(29)}\). The mucous layer is a tissue, a highly viscous product secreted by the goblet cells of the tissue, which coat the epithelial cell surface \(^{(30)}\). The adherent mucus gel lining the alimentary tract has a minimum thickness of ≈40–50 μm and a maximum thickness of ≈300 μm depending on the individual and the region of the alimentary tract \(^{(31)}\). Mucin is the most important glycoprotein of mucus and is responsible for its structure.

The goblet cells of columnar epithelial tissues secrets two types of mucins, *membrane-bound* and *secreted* (soluble) biomacromolecules forming a fully-hydrated viscoelastic gel layer (mucus). Soluble mucins are high-molecular weight glycoproteins (0.5—40 MDa) composed of 500 kDa sub-units linked together by peptide linkages and intra-molecular cystein–cystein disulfide bridges \(^{(32)}\).

Most mucins carry a net negative charge due to the presence of carboxylate groups (sialic acid) and ester sulfates at the terminus of some sugar units (Figure 1.4). The approximate pKa of these acidic groups is 1.0–2.6 resulting in their complete ionization under physiological conditions \(^{(33)}\).
1.4.2. Mucoadhesive Polymers: The application of bioadhesive polymers may be traced back to as far as 1947, when gum tragacanth and dental adhesive powders were combined to form a vehicle for applying penicillin to the oral mucosa\(^{34}\). Later in 1984, Nagai presented his investigation on mucoadhesive material gastro-retentive drug delivery system and proposed an improved treatment for stomatitis by using mucoadhesive tablets. Additionally, an increase in the systemic bioavailability of insulin was observed in the form of bioadhesive powder after nasal administration in dogs\(^{35, 36}\). Thereafter, bioadhesive materials have been used as absorption promoters for several administration routes. Earlier experiments were also done with known polymers available on the market, such as polyacrylic acids. Currently, the latest research is seeking to develop materials that direct the formulation more specifically to the action site and that can offer other functions besides mucoadhesion such as control over permeation within epithelial tissues, and inactivation of enzymes which can compromise release system action\(^{37}\).
Mucoadhesivity of dosage forms is usually achieved by the use of hydrophilic polymers in formulations, which often demonstrate good ability to stick to mucosal membranes. Superior mucoadhesive property is typically observed for polymers possessing non-ionic functional groups or charged groups that is capable of forming hydrogen bonds with mucous membrane \(^{(38)}\). Some of the polymeric structural characteristics necessary for mucoadhesion can be summarized as follows \(^{(39, 40)}\):

(i) Strong hydrogen bonding groups, e.g., carboxyl, hydroxyl, amino- and sulfate groups,

(ii) Strong anionic or cationic charges,

(iii) High molecular weight,

(iv) Chain flexibility,

(v) Surface energy properties favoring spreading onto mucus.

1.4.2.1. First generation mucoadhesive polymers: These materials are natural or synthetic hydrophilic molecules containing numerous organic functions that generate hydrogen bonds such as carboxyl, hydroxyl and amino groups, which do not adhere specifically onto several surfaces. The very first use of mucoadhesive was as denture fixers and the most known examples are carbomers, chitosans, alginates and cellulose derivatives. They can be incorporated into solid formulations, such as tablets, transdermal adhesives and microparticles, and into semisolid formulations including gels, ointments, pastes and suppositories \(^{(27)}\). These polymers can be subdivided into three classes: cationic, anionic and nonionic.

1.4.2.2. Second generation mucoadhesive polymers: Studies on novel mucoadhesive systems involve the use of multifunctional materials. An ideal polymer should exhibit the ability to incorporate both hydrophilic and lipophilic drugs, show mucoadhesive properties in its solid and liquid forms, inhibit local enzymes or promote absorption, be
specific for a particular cellular area or site, stimulate endocytosis and finally to have a
broad safety range. These novel multifunctional mucoadhesive systems are classified as
second generation polymers (40). They are an alternative to non-specific bioadhesives
because they bind or adhere to specific chemical structures on the cell or mucus
surface (27). Good examples of these molecules are lectins, invasins, fimbrial proteins (41),
antibodies (42), and those obtained by the addition of thiol groups to known
molecules (43).

1.4.3. Characteristics of ideal mucoadhesive polymers (44, 45):

i. The mucoadhesive material and its degradation products should be nontoxic
   and non-absorbable from the GI tract.

ii. It should be nonirritant to the mucous membrane.

iii. It should preferably form a strong non-covalent bond with the mucosal
    surfaces.

iv. It should adhere rapidly to soft epithelial tissue and should have some site
    specificity.

v. It must allow easy incorporation of the drug and allow the drug to be released at
   predetermined rate and extent.

vi. The polymer should not decompose or alter its physicochemical properties on
    storage or during shelf life of the drug delivery device.

vii. The polymer should be cost-effective to incorporate in pharmaceutical dosage
    forms.

viii. The polymer should not interfere in drug analysis.

1.4.4. Mucous-Mucoadhesive Interaction (27, 46): Despite several decades of research,
mucoadhesion is still not fully understood. The complexity of interactions between
various polymer-based mucoadhesive dosage forms and biopolymer-based viscoelastic
mucus gel present on the surface of mucosal membranes continues to attract attention of researchers. Numerous studies on developing novel mucoadhesive polymers, mechanisms of their interactions with mucins and mucosal membranes, formulating and administering novel active ingredients via transmucosal routes increasingly appear in the literature (38). In general, for mucoadhesion to occur, bonding between mucoadhesive material and mucin must takes place. These bonding can be formed due to following mechanisms:

- **Ionic bonds:** Where two oppositely charged ions attract each other via electrostatic interactions to form a strong bond.
- **Covalent bonds:** Where electrons are shared, in pairs, between the bonded atoms in order to fill the orbital in both. These are also strong bonds.
- **Hydrogen bonds:** Here a hydrogen atom, when covalently bonded to electronegative atoms such as oxygen, fluorine or nitrogen, carries a slight positively charge and is therefore is attracted to other electronegative atoms. The hydrogen can therefore be thought of as being shared, and the bond formed is generally weaker than ionic or covalent bonds.
- **Van-der-Waals bonds:** These are some of the weakest forms of interaction that arise from dipole–dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non-polar substances.
- **Hydrophobic bonds:** More accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when non-polar groups are present in an aqueous solution. Water molecules adjacent to nonpolar groups form hydrogen bonded structures, which lowers the system entropy. There is therefore an increase in the tendency of non-polar groups to associate with each other to minimize this effect.
1.4.5. **Mechanism of mucoadhesion:** The Mucoadhesive Drug Delivery System (MDDS) must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a MDDS to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water\(^{(40)}\). Thus, the mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage (Figure 1.5). The first stage is characterized by the contact between the MDDS and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer\(^{(37)}\).

1.4.5.1. **Wetting theory:** The wetting theory is perhaps the oldest established theory of adhesion. It is best applied to liquid or low-viscosity bioadhesive. It explains adhesion as an embedding process, whereby adhesive agents penetrate into surface irregularities of the substrate and ultimately harden, producing many adhesive anchors. Free movement of the adhesive on the surface of the substrate means that it must overcome any surface tension effects present at the interface. The wetting theory calculates the contact angle and the thermodynamic work of adhesion\(^{(47)}\). The work done is related to the surface tension of both the adhesive and the substrate, as given by Dupre’s equation\(^{(48)}\) (Eq. 1.1):

\[
\omega_A = \gamma_b + \gamma_t - \gamma_b\nonumber\text{...........................................(Eq. 1.1)}
\]

Where,

- \(\omega_A\) is the specific thermodynamic work of adhesion.
- \(\gamma_b\), \(\gamma_t\) and \(\gamma_b\) is the surface tension of mucoadhesive polymer, surface tension of substrate and the interfacial tension respectively.
The adhesive work done is a sum of the surface tensions of the two adherent phases, less the interfacial tensions apparent between both phases. Figure 1.5 explains the events of a drop of liquid bioadhesive material spreading over a soft-tissue surface.

**Figure – 1.5:** Steps involved in the mucoadhesion process.

Horizontal resolution of the forces gives the Young equation (Eq. 1.2):

\[ \gamma_{ta} = \gamma_{bt} + \gamma_{ba}\cos\theta \]  
\[ \text{……………….. (Eq. 1.2)} \]

Where,

- \( \theta \) is the angle of contact,
- \( \gamma_{bt} \) is the surface tension between the tissue and polymer,
- \( \gamma_{ba} \) is the surface tension between the polymer and air and
- \( \gamma_{ta} \) is the surface tension between tissue and air.

When \( \theta \) is greater than zero, the wetting will be incomplete. But when \( \theta \) will approach zero, and wetting will be complete thus successfully adhere to the biological membrane.

The spreading coefficient, \( S_b \), can be defined as shown in the following equation (Eq. 1.3):

\[ S_b = \gamma_{ta} - \gamma_{bt} - \gamma_{ba} > 0 \]  
\[ \text{………………………….. (Eq. 1.3)} \]

The above equation states that Bioadhesion is successful if \( S_b \) is positive.
1.4.5.2. **Diffusion Theory:** The basis of the “diffusion theory” is chain entanglement between glycoproteins of the mucus and the mucoadhesive polymer. This is a two way diffusion process with penetration rate being dependent upon the diffusion co-efficients of both interacting polymers. Upon initial contact between these polymers, diffusion of the bioadhesive polymer chain into the mucus network creates an entangled network between the polymers. Sufficient polymer chain flexibility, adequate exposure for the surface contact of both polymers, similar chemical structures, and the diffusion coefficient of the bioadhesive polymer are among the factors which influence the inter-diffusion of the macromolecule network. **Figure 1.6,** represents schematic representation of the diffusion theory of adhesion.

![Figure 1.6: Entanglement between glycoproteins and the mucoadhesive polymer chains](image)

1.4.5.3. **Fracture theory:** The fracture theory analyses the force that is required for the separation of two surfaces after adhesion \(^{(49, 50)}\). This assumes that the failure of the adhesive bonds occur at the interface. However, failure normally occurs at the weakest component, which typically a cohesive failure within adhering surfaces \(^{(50)}\).
The maximum tensile strength required for detachment is determined by dividing the maximum force of detachment \( F_m \) by the total surface area \( A_0 \) involved in the adhesion interactions\(^{(49)}\) as shown in Eq. 1.4.

\[
S_m = \frac{F_m}{A_0} \quad \text{(Eq. 1.4)}
\]

In a single component uniform system, the fracture force \( S_f \), which is equivalent to the maximal rupture tensile strength \( S_f \), is proportional to the fracture energy \( g_c \), for Young’s module \( E \) and to the critical breaking length \( c \) for the fracture site, as described in following equation (Eq. 1.5):

\[
S_f \sim \left( \frac{g_c E}{c} \right)^{\frac{1}{2}} \quad \text{…………… (Eq. 1.5)}
\]

Fracture energy \( g_c \) can be obtained from the reversible adhesion work, \( W_r \) and the irreversible adhesion work, \( W_i \). The relationship is expressed in Eq. 1.6:

\[
g_c = W_r + W_i \quad \text{…………… (Eq. 1.6)}
\]

Since, the fracture theory is concerned only with the force required to separate surfaces, it does not take into account the interpenetration or diffusion of polymeric chains\(^{(51)}\).

**1.4.5.4. Mechanical Theory:** Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding
dissipating energy and can be considered the most important phenomenon of the process\textsuperscript{(27, 52)}.

1.4.5.5. **Adsorption theory:** According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in Van-der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions\textsuperscript{(27, 37, 53)}. Such forces have been considered the most important in the adhesive interaction phenomenon \textsuperscript{(27)} because, although they are individually weak, a great number of interactions can result in an intense global adhesion \textsuperscript{(54)}.

1.4.5.6. **Electronic theory:** Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength \textsuperscript{(54)}.

None of these mechanisms or theories alone can explain the mucoadhesion which occurs in an array of different situations. However, the understanding of these mechanisms in each instance can help toward the development of new mucoadhesive products. The mechanisms governing mucoadhesion are also determined by the intrinsic properties of the formulation and by the environment in which it is applied \textsuperscript{(55)}.

1.4.6. **Factors affecting mucoadhesion:** Several factors have been identified to affect the strength and duration of mucoadhesion. The strength of adhesion has been found to change with the initial ‘consolidation’ force applied to the joint, or the length of contact time prior to testing. The presence of metal ions, which can interact with charged polymers, may also affect the adhesion process \textsuperscript{(56)}. Based on the theories of mucoadhesion, several factors those have been affecting Bioadhesion are mentioned below:
1.4.6.1. Physiological factors:

*Mucous turn-over rate and renewal of mucoadhesion surface:* The natural turnover rate of mucin from the epithelial layer is important for at least two reasons: *Firstly* the mucin turnover is expected to decrease the residence time of the mucoadhesive polymer on the mucosal surface. No matter how high is the mucoadhesion strength, the mucoadhesive material will detach from the surface due to high mucin turnover. It have been also demonstrated that mucin turnover rate varies in the presence of mucoadhesive polymers\(^{(57)}\).

*Gastric content and motility:* Presence of food and other concomitant drug administration may affect the mucoadhesion. Peristalsis in the GIT also adversely affects the mucoadhesion system, especially gastro-retentive systems\(^{(58)}\).

*Disease state:* The physicochemical properties of the mucous are known to alter during disease conditions such as the gastric ulcer, ulcerative colitis, inflammatory conditions common cold, cystic fibrosis, bacterial and fungal infections, etc. If the mucoadhesive system to be used in diseased state, the effect of altered physiological condition must be assessed\(^{(49,59)}\).

1.4.6.2. Environmental factors:

*Micro-environmental pH:* pH can influence the surface charge of mucus as well as mucoadhesive polymers. Mucus will have a different charge density depending on pH. At higher pH, the chains are fully expanded due to electrostatic repulsion of carboxylate anions\(^{(60)}\). At higher pH, the chains are fully expanded due to electrostatic repulsion of carboxylate anions.

*Effect of water and/or interstitial fluid:* Presence of water is prerequisite for spreading of mucoadhesive polymer over the surface and create macromolecular network for the interpenetration. However there is a critical level of hydration for
mucoadhesive polymer to achieve optimum swelling & adhesion \(^{(61)}\). Presence of charged metal ions can decrease the number of interaction sites and bonding strength\(^{(58)}\). Concomitant administration of bulk foods, hot food, acidic or alkaline food may affect the mucoadhesion \(^{(60)}\).

*Initial contact time:* Contact time between the mucosal surface and mucoadhesive polymer determines the degree of swelling and interpenetration of the polymer chains. Moreover, mucoadhesive strength increases as the initial contact time increases \(^{(62)}\).

### 1.4.6.3. Polymer related factors:

*Molecular weight:* The optimal molecular weight for maximum mucoadhesion depends on the types of mucoadhesive polymer used and tissue of application \(^{(39)}\). Low molecular weight polymers penetrate well in the mucous layer while higher molecular weight promotes physical entangling. Polymers with higher molecular weight will not moisten quickly to expose free terminal groups for interaction with substrates, while polymers with low molecular weight will for loose gel or dissolve quickly \(^{(63)}\).

*Concentration of active polymer:* There is an optimum concentration for a mucoadhesive polymer to produce maximum adhesion. In a highly concentrated system, the adhesive strength drops significantly because the coiled molecules become separated from the medium, so the chain available for interpenetration becomes limited \(^{(51)}\). When the concentration of the polymer is too low, the number of penetrating polymer chains per unit area of the mucous membrane is small and the interaction between polymer and the substrate is limited \(^{(64)}\).

*Flexibility of polymer chain:* Chain flexibility of mucoadhesive polymeric chain is critical for interpenetration and entanglement. It is necessary for diffusion of chains and entanglement with mucin. For polymers with high level of cross-linking, the motility decreases leading to decrease in mucoadhesion strength \(^{(65)}\). In general, motility
and flexibility of polymeric chain can be related to their viscosities and diffusion coefficients. Higher the flexibility of the polymeric chain, greater the diffusion into the mucous network (66). The increased chain interpenetration can be attributed to the increased structural flexibility of the polymer upon addition of plasticizers, e.g. polyethylene glycol (53).

Cross-linking density: The average the average molecular weight and pore size of the cross-linked polymer and the density of cross-linking are three important and interrelated structural parameters of a polymeric network (67). Therefore it seems that, with increase in density, the swelling of the polymer decreases which may leads to limit the interpenetration between polymer and mucin (65). It was reported that, this is general property of polymers, in which the degree of swelling at equilibrium has an inverse relationship with the degree of cross-linking of a polymer (67).

Swelling / Hydration capacity: Hydration is prerequisite for a mucoadhesive polymer to expand and create a proper ‘macromolecular mesh’ of sufficient size and to induce the mobility of the polymeric chain in order to enhance the interpenetration process between polymer and mucin. Over hydration results in the formation of a wet slippery mucilage without adhesion (51). However, a critical degree of hydration of the mucoadhesive polymer exist where optimum swelling and adhesion occurs (61).

Charge: The charge of polymer is an important element for bioadhesion (68). The strength of mucoadhesion of polymers with carboxyl groups was much stronger than that of those with neutral groups (69). The strong anionic charge on the polymer is one of the required characteristics for mucoadhesion (39).

Bonding capacity: Hydrogen bonding is another important factor for successful mucoadhesion of a polymer. For mucoadhesion to be occurred, polymer must have functional groups that are able to form hydrogen bonds (66). Ability to form hydrogen
bonds is due to the presence of functional groups such as COOH, OH etc. Flexibility of the polymer may also attribute to its improved hydrogen bonding \(^{(39,70)}\).

1.4.7. Application of Oral Mucoadhesive Drug Delivery Systems\(^{(25)}\): In general, oral mucoadhesive drug delivery systems are capable of adhere to the gastric mucosa to release the drug at upper GIT. This phenomenon of the gastro-retention of the MDDS can be exploited for following applications:

1.4.7.1. Enhancement of bioavailability: Drugs absorbed from a narrow absorption window in stomach region characterized by poor bioavailability. Bioadhesion to the gastric mucosa provide longer residence time for the drug to be available at the site of absorption.

1.4.7.2. Reduced frequency of dosing: For drugs with relatively short biological half-life, sustained and slow input from CR-MDDS may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapeutic outcome \(^{(29)}\).

1.4.7.3. Minimized Adverse effect: Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the distal intestinal part. Thus, undesirable activities of the drug in colon may be prevented.

1.4.7.4. Extended time for effective concentration: For certain drugs that have non-concentration dependent pharmacodynamics, the clinical response is not associated with peak concentration, but rather, with the duration of time over a critical therapeutic concentration

1.4.8. Suitability of drug candidate for MDDS:

- Narrow absorption window in GI tract.
- Primarily absorbed from stomach and upper part of GIT.
- Drugs that act locally in the stomach.
• Drugs that degrade in the colon.

• Drugs that disturb normal colonic bacteria.

• Drugs with considerable solubility and stability in acidic pH.

1.5. POLYSACCHARIDES IN DRUG DELIVERY SYSTEMS:

Polysaccharides are among the most widespread organic compounds in the plant kingdom. They are typically complex carbohydrate biopolymers composed of monosaccharide units linked together by glycosidic bonds into linear or branched chains of different length \(^{(71)}\) (Figure 1.8). Polysaccharide is the name given to a macromolecule consisting of a large number of monosaccharide residues joined to each other by glycosidic linkages \(^{(72)}\).

![Molecular structure of polysaccharide.](image)

**Figure – 1.8:** Molecular structure of polysaccharide.

Polysaccharides are present in huge quantities in varieties of plants, animals, marine and microbial sources. Plant polysaccharides are very common with different structural and metabolic functions commonly found in family Leguminosae, Sterculiaceae, Bixaceae, Compositae, Combretaceae, Gigarginaceae. Polysaccharides
composed of only one kind of monosaccharide are described as *homopolysaccharides* e.g. Amylose, Cellulose etc. Similarly, if two or more different kinds of monomeric unit are present, the class name *heteropolysaccharide* e.g. Arabin, Carrageenan, Gallan etc. may be used. Polysaccharides can also be classified according to their molecular shape: *Linear Polysaccharide:* e.g. Algin, Amylose, Cellulose etc. *Branched Polysaccharide:* Short branched: e.g. Arabinans, galactomannan, Xylan, Xanthan etc. *Branch-on-branch:* e.g. Amylopectin, gum tragacanth etc.

1.5.1. Advantages of natural polysaccharides: 

- **Non-toxic and biocompatible:** All polysaccharides are composed of repeating units of natural monosaccharide molecules, therefore, they are non-toxic.

- **Biodegradable:** Naturally occurring biodegradable polymers are product of living organisms. They are found to be truly renewable source no or least adverse impact on humans or environmental health.

- **Low cost:** Due to natural abundance, they are cheaper in cost. The processing cost is also much lower compared to synthetic material.

- **Environmental-friendly processing:** Collection and processing of these natural substances do not involve any environmentally hazardous process.

- **Local availability:** Local cultivation and availability of polysaccharide makes important contribution in economic development.

- **Better patient tolerance as well as public acceptance:** There is relatively fewer incidences of side and adverse effects with natural materials compared with synthetic one.

- **Edible sources:** Many of the polysaccharides are obtained from edible natural sources. Hence well accepted by consumers’ leads to better compliance.
1.5.2. Disadvantages of natural polysaccharide\(^{(73)}\):

- **Microbial contamination**: Presence of relatively higher proportion of equilibrium moisture content in the natural polysaccharides makes them prone to the chance of microbial contamination. However, this can be prevented by proper harvesting, processing and storage.

- **Batch to batch variation**: Synthetically obtained materials are manufactured in a controlled procedure with fixed quantities of ingredients, while the biosynthetic production of natural polysaccharide is dependent on environmental and seasonal factors.

- **Uncontrolled rate of hydration**: Due to differences in the harvesting, collection and processing of natural materials at different times, as well as differences in region, species, and climatic conditions the proportion of chemical constituents present in a given material may vary.

- **Alteration of viscosity on storage**: Due to the complex chemical nature of polysaccharides (monosaccharide composition, chain length, cross-linking etc.), it has been found that after long term storage there is alteration in viscosity.

1.5.3. Properties of polysaccharides:

1.5.3.1. Physical Properties: The physical properties of polysaccharides depend on their monosaccharide composition, glycosidic linkage, functional groups, molecular size and branching.

- **Solubility**: Unmodified polysaccharides are generally readily soluble in aqueous solvents. Highly crystalline polysaccharides (e.g. cellulose), highly branched or cross-linked polysaccharides (e.g. starch) are often insoluble in aqueous solvents. There are few organic solvents that can dissolve these unmodified polysaccharides. Polar solvents capable of hydrogen bonding interaction such as formaldehyde,
dimethylformaldehyde, dimethyl sulfoxide, pyridine are most commonly used to solubilize polysaccharides.

- **Viscosity and surface activity:** Polysaccharides are among the most viscous natural products. The viscosity of a polysaccharide increases with its chain length or molecular weight. Polysaccharides do not lower the surface tension of aqueous solutions, but affinity for oil-water interface they are useful as emulsifiers.

- **Crystallinity:** Polysaccharides have wide range of crystallinity. Most polysaccharides are not readily crystallized and are often isolated as amorphous solids. The difficulty in crystallizing polysaccharides results from their conformational flexibility.

- **Hygroscopicity:** Many polysaccharides are hygroscopic, often containing substantial amount of water even after extensive drying efforts.

- **Stability:** Polysaccharides are generally fairly stable molecules. However presence of reducing sugars makes them sensitive to oxidation. Many polysaccharides also contain acid-sensitive glycosidic-linkage which may leads to acid hydrolysis of the polymeric chain. Elevated temperature, altered pH, addition of denaturant also affects the stability of polysaccharides.

- **Optical activity:** Most polysaccharides can absorb little light in either ultraviolet or visible spectral region. Virtually most polysaccharides contain multiple chiral centers and thus they are optically active.

**1.5.3.2. Chemical properties:** The chemical properties of polysaccharides depend on the monosaccharide residue present, their functional groups, the linkage positions and configuration.
Evaluation and optimization of mucoadhesive drug delivery of famotidine with polysaccharide isolated from *Hibiscus esculentus* Linn.

Chapter 1

Introduction

- **Hydrolysis:** The most frequently occurred chemical transformation of polysaccharides is acid-catalyzed hydrolysis to cleavage the glycosidic linkage. Autohydrolysis often take place in normal storage condition.

- **Oxidation and reduction:** Polysaccharides are relatively insensitive to oxidation-reduction. In presence of stronger oxidants in severe environmental condition, polysaccharides may undergo oxidation reaction.

- **Chelation and complexation:** Many natural polysaccharides and their derivatives show affinity towards various classes of metal ions. Anionic groups such as carboxylate, $O$-sulpho and $O$-phospho are often capable of forming chelates with metal ions. Polysaccharides are often form complexes with a wide range of molecules.

1.5.4. Application of Polysaccharides: Polysaccharides from different sources and their derivatives represent a group of polymers widely used in pharmaceutical industry. They found diverse and widespread application in the food, beverage and cosmetic industry and are regarded as safe for human consumption.

1.5.4.1. Pharmaceutical Excipients: The specific application of natural polysaccharide polymers in pharmaceutical formulations include to aid in the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use (74).

- **Binding agent:** A number of plant polysaccharides are being used commercially as binding agents in tablet formulations. Starch, acacia, tragacanth and cellulose derivatives are being used commercially since ancient days. Polysaccharide of
Evaluation and optimization of mucoadhesive drug delivery of famotidine with polysaccharide isolated from *Hibiscus esculentus* Linn.
1.5.4.2. **Release retardant in solid dosage forms:** Polysaccharides obtained from plant, animals and marine sources have been shown to be useful for the construction of drug delivery systems. Regular research is going on in the field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration. Xanthan gum\(^\text{(95)}\), \textit{H. esculentus} polysaccharide\(^\text{(86)}\), guar gum\(^\text{(89)}\), karaya gum\(^\text{(84)}\) etc are among many of those polysaccharides evaluated as release retardant for solid dosage form.

1.5.4.3. **Targeted delivery of drugs:** Polysaccharides due to their versatile and complex molecular structure, have found their application in targeted delivery of drugs. Pectin\(^\text{(96)}\), chitosan\(^\text{(97)}\), tamarind seed polysaccharide\(^\text{(98)}\), guar gum\(^\text{(99)}\) etc have successfully reported to be used in drug delivery to colon.

1.5.4.4. **Mucoadhesive drug delivery:** Natural polysaccharides and their derivatives, due to high viscosity, swelling properties and chain flexibility found wide application in mucoadhesive drug delivery. Tamarind seed polysaccharide\(^\text{(100)}\), sodium alginate\(^\text{(100)}\), gum karaya\(^\text{(101)}\), \textit{Hakea gibbos}a polysaccharide\(^\text{(103)}\) etc have been successfully evaluated as mucoadhesive carrier.

1.5.4.5. **Gelatin replacement for Hard Capsules Shell:** Hard capsule shells prepared with polysaccharide are known as “Vegetable Capsule shell”. Starch, tamarind seed polysaccharide, carrageenan, pectin, gallan gum, algae polysaccharide etc. have been studied for preparation of hard capsule shells. Satisfactory results of these studies leads to commercial product like ‘Quali-V’\(^\text{®}\) Shionogi Qualicaps Co, Japan\(^\text{(104,105)}\).

1.5.4.6. **Breast Implants:** Polysaccharides have been reported to be used as an alternative to silicone breast implants. The implants, also known as “Poly-Implants”, are
made of a silicone elastomer shell filled with polysaccharide gel for augmentation of breast. Viscoelastic properties and biodegradability are among many advantages of the polysaccharide over conventional silicone-filled breast implants.\(^{(106)}\)

1.5.4.7. **Biodegradable packing materials:** Bio-polymeric materials such as polysaccharides getting much interest for commercial production of biodegradable and economical packaging materials for food, cosmetic and pharmaceutical products. Starch, cellulose and many other polysaccharides and their derivatives are being studied as bioplastic material.

1.5.4.8. **Medical Textiles:** Cellulose is the most used natural fiber for medical textile as bandages. Dextrin, starch etc. have also been reported as potential candidate for bandages. Chitosan is well known hemostatic agent for hemostatic bandages for trauma care to control sever bleeding.

1.5.4.9. **Additives for Food industry:** Natural polysaccharide and their derivatives have a variety of applications in the food and beverage industry. Different gummy polysaccharides have different uses like water retention and stabilization, stabilizers for ice-cream, meat products and instant pudding, dairy, confectionary and meat products, confectionary, beverages, backed product, and sauces.\(^{(107)}\)

1.5.5. **Polysaccharide in Mucoadhesive Drug Delivery Systems:**

Over the years polysaccharides and their derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxyl propyl methylcellulose, hydroxyl propyl cellulose, xanthan gum, gellan gum, guar gum, and carrageenan have found their applications in mucoadhesive drug delivery systems.\(^{(108)}\) (Table 1.1). Their favorable molecular, physicochemical and biological characteristics make them suitable choice for mucoadhesive drug delivery systems.
Table – 1.1: Some commercially available mucoadhesive drug delivery systems using polysaccharide as mucoadhesive material.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Bioadhesive material used</th>
<th>Pharmaceutical Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccastem</td>
<td>Reckitt Benckiser</td>
<td>PVP, Xanthan gum, Locust bean gum</td>
<td>Buccal Tablet</td>
</tr>
<tr>
<td>Corlan Pellets</td>
<td>EllTech</td>
<td>Acacia gum</td>
<td>Oromucosal pellets</td>
</tr>
<tr>
<td>Suscard</td>
<td>Forest</td>
<td>HPMC</td>
<td>Buccal tablet</td>
</tr>
<tr>
<td>Gaviscon liquid</td>
<td>Reckitt Benckiser</td>
<td>Sodium alginate</td>
<td>Oral Liquid</td>
</tr>
<tr>
<td>Orabase</td>
<td>Conva Tech</td>
<td>Pectin, Gelatin</td>
<td>Oral paste</td>
</tr>
<tr>
<td>Corsodyl gel</td>
<td>Glaxo Smith Kline</td>
<td>HPMC</td>
<td>Oromucosal gel</td>
</tr>
<tr>
<td>Timoptol – LA</td>
<td>Merck</td>
<td>Gallan gum</td>
<td>Eye gel</td>
</tr>
<tr>
<td>Aci-jel</td>
<td>Janseen – Cilag</td>
<td>Tragacanth and Acacia</td>
<td>Vaginal gel</td>
</tr>
<tr>
<td>Gynol – II</td>
<td>Janseen-Cilag</td>
<td>Na CMC and PVP</td>
<td>Vaginal gel</td>
</tr>
</tbody>
</table>

1.6. OPTIMIZATION AND DESIGN OF EXPERIMENT:

1.6.1. Optimization: The term ‘optimization’ has been defined as ‘the implementation of systemic approach to achieve the best combination of product and / or process characteristics under a given set of condition’\(^{(111)}\). Simply optimization of drug formulations or pharmaceutical processes is a phenomenon of finding the best possible composition or operating condition. Since decades, development and optimization of pharmaceutical dosage form or processes related to it are being conducted by trial and error method. This approach of trial and error methodology for developing new dosage
form or modifying existing formulations was solely based on the knowledge, previous experience and wisdom of formulator.

Figure – 1.9: Steps involved in optimization of Pharmaceutical dosage forms

In Pharmaceutical fields the formulations are not usually simple systems. They often contain many ingredients and variables which may interact with one another to produce unexpected and unexplainable results. The development of a solid, semisolid or liquid formulation and the associated process usually involves a number of variables. Mathematically, they can be divided into two groups — independent and dependent. The independent variables are the formulation and process variables directly under the control of the formulator. These might include the level of a given ingredient or the parameter for a given process step. The dependent variables are the responses or the characteristics of the resulting product. These are a direct result of any change made in the formulation or process (112). The traditional approach of optimizing a formulation or process essentially entails studying the influence of the corresponding composition and process variable by changing ‘one variable at a time’ while keeping others constant. The
modern formulation optimization approaches employs systemic Design of Experiments (DoE). The application of mathematical optimization in the pharmaceutical field was first reported by Fonner et al. Later developments in the computer science have enabled the incorporation of the optimization algorithm into the experimental design software\(^\text{(113)}\).

1.6.2. Design of Experiment (DoE): Conduct of an experiment and subsequent interpretation of its experimental outcome are the twin essential features of the general scientific methodology\(^\text{(114, 115)}\). This can be accomplished only if the experiments are carried out in a systematic way and the inferences are drawn accordingly. An experimental design is the statistical strategy for organizing the experiments in such a manner that the required information is obtained as efficiently and precisely as possible\(^\text{(114, 116)}\). Runs or trials are the experiments conducted as per the selected experimental design\(^\text{(117, 118)}\). Such DoE trials are arranged in the design space in such a way that reliable and consistent information is achievable with minimum experimentation. The layout of the experimental runs in a matrix form, as per the experimental design, is known as design matrix\(^\text{(119)}\). Computer-based systematic design and optimization techniques have widely been practiced these days. Such techniques are usually referred to as 'Computer-Aided Dosage Form Design' (CADD). Their implementation invariably includes the statistical design of experiments (DoE), generation of mathematical equations and graphic outcomes, thus depicting a complete picture of variation of the response(s) as a function of the factor(s)\(^\text{(115, 118, 120)}\). DoE optimization methodologies can be categorized into two classes:

- **Simultaneous optimization**, also popularly known as Response Surface Methodology (RSM) where the experimentation is completed before the optimization takes place. Simultaneous optimization approach is a model dependent technique\(^\text{(118)}\). The key
elements in its implementation encompass the experimental designs, mathematical models and the graphic outcomes. One or more selected experimental responses are recorded for a set of experiments to predict an optimum and the interaction effects. This is followed by the determination of the mathematical model for each response in the zone of interest, i.e., the experimental domain.

**Sequential optimization**, where experimentation continues sequentially as the optimization study proceeds \(^{(115, 120)}\). In sequential approach, optimization is attempted in a step-wise fashion. Experimentation is started at an arbitrary point in the experimental domain and responses are evaluated. Subsequent experiments are designed based upon the results of these studies, according to an algorithm that directs newer experiments towards the optimum. Whether the chosen optimum is a maximum or a minimum, the general term used for this approach is "hill climbing" \(^{(118, 119)}\). An important aspect of sequential designs is to know when the goal has been accomplished.

Choice of an experimental design amongst various available options depends on the amount of resources available and degree of control over making decisions. It is important to understand the complexity of dosage forms and pharmaceutical processes by using established statistical tools. The designs used for the simultaneous optimization for the execution of RSM include:

A. Factorial Design (FD).

B. Central Composite Design (CCD).

C. Mixture Design.

D. D-optimal Design.

1.6.2.1. **Factorial Design**: Factorial designs are most frequently used DoE for optimization of pharmaceutical formulations and processes. A factorial design produces three important pieces of information; the simple effects, the interaction effects, and the
main effects. The number of experiments required for the study is dependent on the number of independent variables selected and their levels \(^{(121)}\). Factorial designs are two types namely, Full Factorial Design and Fractional Factorial Design. These are generally based upon first-degree mathematical models \(^{(117)}\). Full FDs involve studying the effect of all the factors (n) at various levels (x), including the interactions amongst them, with the total number of experiments as \(x^n\). The mathematical model associated with a two level two factor full factorial design is postulated as following (Eq. 1.7):

\[
Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 \ldots \quad \text{(Eq. 1.7)}
\]

1.6.2.2. Central Composite Design: A Central Composite Design (CCD) comprises of two level factorial points, axial or star points and a central point. The total number of runs or experiments is expressed by \((2^n + 2n + 1)\). The axial points for two factor design \((\pm \alpha, 0)\) and \((0, \pm \alpha)\) where, \(\alpha\) is the distance of the axial points and central point. The mathematical model associated with a two level two factor full factorial design is postulated as following (Eq. 1.8):

\[
Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \varepsilon \ldots \quad \text{(Eq. 1.8)}
\]

1.6.2.3. Mixture Design: If in a pharmaceutical formulation, characteristics of the finished product are not dependent on the quantity of each ingredient but on their proportion, a Mixture design is highly recommended. In two-composition mixture, one factor level can be independently varied at a time. The mathematical model for estimating the effects of mixture design is expressed as follows (Eq. 1.9):

\[
Y = \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 \ldots \quad \text{(Eq. 1.9)}
\]

1.6.2.4. D-Optimal Design: The optimal design method requires a correct model is postulated, the variable space defined and the number of design points fixed in such a way that will determine the model coefficients with maximum possible efficiency. One
of the ways of obtaining such a design is by the use of exchange algorithms using computers \cite{119,122}. D-optimal designs are also used for screening of factors. Depending upon the problem, these designs can also be used along with factorial, central composite and mixture designs.

1.6.3. Selection of DoE: Box & Draper stated “All models are wrong, but some are useful”. Success and failure of an optimization design is subsequently depends on the judicious selection of proper model. In general, a model has to be proposed before the start of the DoE optimization study \cite{123}. Model selection depends upon the type of the variables to be investigated and the type of the study to be made, i.e., factor screening, description of the system, or prediction of the optima or feasible regions. The choice also depends on the prior knowledge and wisdom of the experimenter about possible interactions and quadratic effects \cite{118}. It is a good idea to choose a design that requires fewer runs to save the time and permit the budget. Selection of a low resolution and simple design will not allow investigating the higher order interactions and effect while selection of a high resolution complicated design may leads to over fitting of too large number of data. One or more of the model diagnostic plots can be plotted to investigate the goodness of fit of the proposed model. These plots includes, Actual vs. Predicted plot, Residual vs. Predicted plot, Residual vs. Run plot, Residual vs. Factors plot, Normal-Probability plot, Half-Normal plot etc.

1.6.4. Search for the Optimum Formulation: Optimization of one response or the simultaneous optimization of multiple responses can be accomplished either numerically or graphically.

1.6.4.1. Numerical Optimization: When the effects of the independent variables to be investigated on a large number of responses, mathematical or numerical optimization is preferred. Each response associated with its own desirability functions. To overcome
the difficulty of multiple or opposing responses, desirability function is used. The objective function is used to find an optimum formulation, either for a minimum or a maximum in the presence of inequality or equality.

1.6.4.2. Graphical Optimization or Response Surface Methodology (RSM): Response Surface Methodology can be defined as a “statistical method that uses quantitative data from appropriate experiments to determine & simultaneously solve multivariate equations”. The RSM has widely been used for optimization and selecting acceptable pharmaceutical formulations. At the completion of DoE trial runs as per the chosen statistical design, a series of data on response variables are obtained. Such data can be suitably modeled to generate mathematical relationship between the independent variables and the dependent variable. Graphical depiction of the mathematical relationship is known as response surface (118, 124). A response surface plot is a 3-D graphical representation of a response plotted between two independent variables and one response variable. The use of 3-D response surface plots allows understanding of the behavior of the system by demonstrating the contribution of the independent variables. One or more of the following methods can be employed to optimize a formulation:

a) Search Method: These methods are employed for choosing the upper and lower limits of the responses of interest (120). In these search methods, the response surfaces, as defined by the appropriate equations, are searched to find the combination of independent variables yielding the optimum. Two major steps are used viz. feasibility search and grid search. Together, these techniques are also referred to as brute force method (117, 118). The feasibility search method is used to locate a set of response constraints that are just at the limit of possibility. One selects several values for the responses of interest and a search of the response surface is made to determine whether
a solution is feasible. The feasibility search method yields the possibilities satisfying the constraints. Subsequently, the exhaustive grid search is applied, wherein the experimental range is divided into a grid of specific size, and searched methodically. Grid search method can provide a list of possible formulations and the corresponding response values.

b) **Overlay Plot:** The response surfaces or contour plots are superimposed over each other to search for the best compromise visually. Minimum and maximum boundaries are set for acceptable objective values. The region is highlighted where all the responses are acceptable. Within this area, an optimum is located, trading off the different responses. The use of overlay diagrams is limited only to three or four response variables \(^{(115, 118)}\).

### 1.7. PLANT PROFILE – *Hibiscus esculentus* Linn.

**1.7.1. Synonyms\(^{(125)}\):** *Abelmoschus esculentus* Linn., Lady’s finger (Eng.), Bhindi (Hindi), Dheras (Bengali), Okra, Gumbo (French), Bhenda (Sanskrit), Vandakkai (Malayalam).

**1.7.2. Biological Source\(^{(126)}\):** *Hibiscus esculentus* Linn. belonging to the family: Malvaceae.

**1.7.3. Taxonomical Details:**

- **Kingdom** : Plantae – Plants
- **Subkingdom** : Tracheobionta – Vascular plants
- **Superdivision** : Spermatophyta – Seed plants
- **Division** : Magnoliophyta – Flowering plants
- **Class** : Magnoliopsida – Dicotyledons
- **Subclass** : Dilleniidae
1.7.4. Description: Erect, stout, annual herbs or undershrubs, 0.5-2 m high; stem and branches scattered with short stiff simple-hairs, ultimately glabescent; Leaves cordate at base, ovate-orbicular, 4-20 x 4-25 cm; open, coarsely toothed; petioles 4-30 cm long, accrescent up to 5 cm, bristly hairy; stipules linear subulate, 2-2.5 cm long, entire or 2-fid; epicalyx segments 7-10, 5-10 x 1-2.5 mm. Matured unripen fruits, commonly known as pods, may be harvested 60-180 days from sowing about 5-10 days after flowering depending on the cultivar grown. Successional harvesting of young pods is generally recommended. The fruits are up to 20 cm long, pyramidal-oblong, creamy green to dark green in colour, with longitudinal edges and hairy surfaces (Figure 1.10 and 1.11). The pods are harvested by detaching using a slight twist to break the stalk. The fresh and green tender fruits are used as vegetable. The mucilage content is highest in fresh and tender fruits.

1.7.5. Habitat: The plant is considered to be African or Asian in origin and is valued for its edible pods. It is grown as garden crop or home-yard plant throughout tropical and subtropical parts of the world. It is found cultivated throughout India up to an altitude of 4000 ft.

1.7.6. Chemical Composition: The fruits are chiefly consists of mucilage, protein and fibers. The fresh and tender fruit of *H. esculentus* consists of 88% moisture, 7.7% carbohydrate, 2.2% protein, 1.2% fibers, and traces of other minerals including iron, calcium, magnesium, phosphorous, copper manganese etc. The mucilage of the

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Chapter: 1

**Introduction**

- **Order**: Malvales
- **Family**: Malvaceae – Mallow family
- **Genus**: Hibiscus Medik. – okra
- **Species**: *Hibiscus esculentus* (L.) Moench – okra
fruits reported to contain soluble sugars and polysaccharides. The acid hydrolysis of mucilage yields \( d \)-galactose, \( d \)-glucose, \( l \)-rhamnose, \( l \)-arabinose and \( d \)-galactouronic acid. The crude mucilage also contains about 9.2% protein \(^{(131)}\). Woolfe et al in their study reported that the polysaccharide composition in partially purified is similar as that of pectin.

**Figure – 1.10:** *Hibiscus esculentus* Linn. Plant.

**Figure – 1.11:** Unripe fresh fruits of *Hibiscus esculentus* Linn.

1.7.7. Uses: Bhindi or Ladies finger is a common vegetable for a wide population across the world. The fresh fruits, leaves, stem, roots and seeds found their way in kitchen for food delicacy since time immemorial.

- The fibers of the fruits, which chiefly consists of cellulose, can be spun into yarn and ropes. The seeds contain 22% edible oil\textsuperscript{130}.
- The mucilage been also used as clarifying agent for sugarcane juice in ‘gur’ manufacturing.
- The mucilage has been successfully investigated as plasma replacement or blood volume expander in experimental animals.
- The dried mucilage reported to be a potential excipient for pharmaceutical preparation.

1.8. DRUG PROFILE – FAMOTIDINE:

Famotidine is a competitive histamine H\textsubscript{2}–receptor blocker. It inhibits both diurnal and nocturnal basal gastric acid secretion elicited by histamine and other H\textsubscript{2} antagonist in a dose-dependent and competitive manner. In humans, famotidine inhibits basal and stimulated gastric acid secretion from parietal cells and has no apparent clinically significant activity at histamine H\textsubscript{2}-receptors outside the gastrointestinal tract. Through the inhibition of gastric acid secretion, famotidine promote the healing of duodenal and gastric ulcers and erosive esophagitis. Famotidine is given by mouth or parenterally by the intravenous route. It has an excellent tolerability profile and has the lowest incidence of side effects\textsuperscript{132}.

1.8.1. General Information\textsuperscript{133}:

1.8.1.2. Marketed Dosage forms: Tablets 20 mg & 40 mg, Injection 20 mg, Oral Suspension 40 mg/5 ml.

1.8.1.3. Proprietary names: Amfamox; Brolin; Dispromil; Famodil; Famodine; Famosan; Famosal; Ganor; Gastor; Gastropen; Ifada; Lecedil; Motiax; Pecid; Pecdicyc; Pecdidin; Pecdine; Pecp; Pecdul; Ulcusan; Ulfinol.

1.8.2. Chemistry:

1.8.2.1. Chemical Name\(^{134}\): 3-[[2-[(Aminoimino)methyl] amino]-4-thiazolyl] methyl thio]-N-(aminosulfonyl) propanimidamide.

1.8.2.2. Molecular formula\(^{134}\): \(\text{C}_{8}\text{H}_{15}\text{N}_{7}\text{O}_{2}\text{S}_{3}\)

1.8.2.3. Chemical Structure:

![Chemical structure of famotidine](image)

Figure – 1.12: Chemical structure of famotidine

1.8.2.4. Molecular weight: 337.5

1.8.3. Physicochemical properties\(^{134, 135}\): Famotidine is white to pale yellowish white crystalline powder with characteristic odour.

1.8.3.1. Melting Point: 163°C to 164°C.

1.8.3.2. Solubility: It is very slightly soluble in water (0.1% at 20°C) and dehydrated alcohol; practically insoluble in acetone, alcohol, chloroform (< 0.01%, 20°C), ether and ethyl acetate (< 0.01%, 20°C); slightly soluble in methyl alcohol; freely soluble in dimethylformamide (80%, 20°C) and glacial acetic acid (50%, 20°C). It dissolves in dilute mineral acids.
1.8.3.3. **pH:** Famotidine solution has a pH of 5.0 – 5.6; homogenous suspensions of the drug have a pH of 6.5 – 7.5.

1.8.3.4. **Dissociation Constant:** pKa 7.06

1.8.3.5. **Partition Coefficient:** Log P (octanol/water) = 0.64

1.8.3.6. **Storage:** Famotidine is photosensitive and degrades upon exposure to light hence to be Stored in well-closed, light resistant container.

1.8.4. **Pharmacology:**

1.8.4.1. **Mechanism of action:** Famotidine inhibits acid secretion by reversibly competing with histamine for binding to H₂ receptors on the basolateral membrane of parietal cells. Famotidine predominantly inhibit basal acid secretion, which accounts for their efficiency in suppressing nocturnal acid secretion. It also inhibits the basal and nocturnal acid secretion stimulated by caffeine, food and prostaglandin. Because the most important determinant of duodenal ulcer healing is the nocturnal acidity, evening dosing of famotidine is adequate in most instances.

1.8.4.2. **Indications and usage:**

- **Short-term treatment of active duodenal ulcer.** Clinical studies revealed that most adult patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.

- **Maintenance therapy for duodenal ulcer:** Famotidine at reduced dosage may be continued after healing of an active ulcer. Controlled studies in adults have not extended beyond one year.
• **Short-term treatment of active benign gastric ulcer:** Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

• **Short-term treatment of gastroesophageal reflux disease (GERD):** Famotidine is indicated for short term treatment of patients with symptoms of GERD. It is also indicated for the short-term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy.

• **Treatment of pathological hypersecretory conditions:** For example Zollinger-Ellison Syndrome, multiple endocrine adenomas.

1.8.4.3. **Adverse drug reactions** (139): Famotidine shows rare occurrence of adverse reactions. Generally observed side effects include headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%). Approximately 1% of patients reported to the occur following side effects:

• **Cardiovascular:** Arrhythmia, AV block, palpitation have been reported.

• **Hypersensitivity:** Anaphylaxis, angioedema, orbital or facial edema, urticarial, rash etc. have found in fewer cases.

• **Nervous system:** Grand mal-seizure, reversible psychic disturbances, hallucination, confusion, anxiety have been reported by some patients receiving famotidine.

1.8.4.4. **Drug interactions** (141, 142):

• **Tizanidine:** Concomitant administration of Famotidine with Tizanidine may significantly increase the blood levels and effects of Tizanidine. This may cause blood pressure to fall excessively. The risk of other side effects such as drowsiness, dizziness, lightheadedness, and fainting may also increase.

• **Atazanavir:** Famotidine decrease plasma level of Atazanavir.
• **Enoxacin**: Famotidine decreases the absorption and systemic availability of Enoxacin.

• Presence of food slightly increases the bioavailability of famotidine. Alcohol and caffeine reported to interact with famotidine.

1.8.5. **Pharmacokinetics** (133, 142): The recommended famotidine dose to achieve those gastrointestinal effects is 40 mg daily at bedtime for 4–8 weeks, and these doses produced peak plasma concentrations of 75–100 ng/ml. Plasma famotidine concentrations that inhibit 50% of stimulated gastric acid secretion, that is, IC50, are estimated to be 13 ng/ml. The duration of inhibition of basal and nocturnal acid secretion following an oral dose of the drug is 10–12 h. Inhibition of food-stimulated secretion generally persists for 8–10 h. The summary of pharmacokinetic parameters of Famotidine in presented in Table 1.2:

**Table – 1.2**: Pharmacokinetic parameters of Famotidine at 40mg daily dose.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Pharmacokinetic Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Absorption</td>
<td>Rapid but incomplete</td>
</tr>
<tr>
<td>2.</td>
<td>Fraction Bioavailable (%)</td>
<td>20 – 45%</td>
</tr>
<tr>
<td>3.</td>
<td>Elimination half-life (h)</td>
<td>2.5 – 3.5</td>
</tr>
<tr>
<td>4.</td>
<td>Volume of distribution (lit/Kg)</td>
<td>0.94 – 1.33</td>
</tr>
<tr>
<td>5.</td>
<td>Protein Binding (%)</td>
<td>15 – 22%</td>
</tr>
<tr>
<td>6.</td>
<td>Clearance (lit/min)</td>
<td>0.19 – 0.43</td>
</tr>
<tr>
<td>7.</td>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>75 – 100</td>
</tr>
<tr>
<td>8.</td>
<td>( T_{\text{max}} ) (hr)</td>
<td>3</td>
</tr>
<tr>
<td>9.</td>
<td>Steady-state plasma conc.(mg/lit)</td>
<td>0.02 – 0.06</td>
</tr>
</tbody>
</table>
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