1 Controlled Release and Gastroretentive Drug Delivery Systems

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Over the past decades we have witnessed the availability of wide range of controlled release dosage forms in the pharmaceutical market. There are several reasons for the attractiveness of these dosage forms, such as, reduced dosing frequency, patient compliance, improved dissolution profiles, and maintenance of the peak plasma concentration for prolonged time period. The performance of a controlled release delivery system depends on:

(a) Drug release from the dosage form (dissolution)
(b) Movement of the drug within the body

The dissolution process involves two steps, an initial detachment of drug molecule from the solid bulk surface to the adjacent liquid interface, followed by the diffusion of drug molecule from the solid-liquid interface into the bulk liquid medium. The dissolution of dosage form depends on the dosage form fabrication and physicochemical properties of the drug molecule. Movement of the drug within the body depends on pharmacokinetics of the drug.

Based on the formulation technologies, controlled release drug delivery systems can be classified as activation-modulated, diffusion controlled, dissolution controlled, feedback-regulated, site-targeted, or stimuli-sensitive delivery systems. Diffusion controlled or dissolution

controlled systems are the most common controlled release systems. Diffusion controlled systems are either matrix type or reservoir type; whereas dissolution controlled systems are encapsulated systems, matrix systems or multi-layer matrix tablets. This chapter will consider the basic approaches used in the development and kinetic modeling of diffusion and dissolution controlled delivery systems. Further the chapter will give a laconic overview of various controlled release gastroretentive drug delivery systems.

1.1 Diffusion

Diffusion process is related to the intermixing of molecules as a result of random motion caused by molecular kinetic energy. Mixing of water soluble dye in a water filled beaker is the simplest example explaining the diffusion process. The dye molecules diffuse throughout the water beaker resulting in a uniform colour. At equilibrium, when a uniform colour exists throughout the water due to the equal distribution of dye molecules, no further net movement is observed (Fig. 1.1). The same case can be observed in the diffusion of drug molecule in our body. The process of transport of a drug through a polymer carrier can be well explained by Fick's laws of diffusion, which are derived by Adolf Fick in 1855. Fick's first and second law are applied to asses flux and drug concentration across the biological membrane.

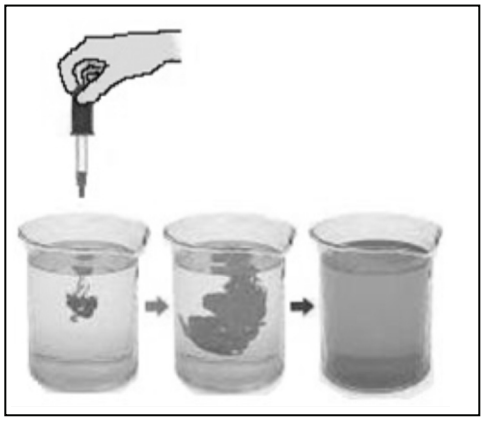

FIGURE 1.1 Process of colour diffusion in water system.

1.1.1 Fick's First Law of Diffusion

Fick's first law postulates that, under the assumption of steady state, the flux goes from a region of higher concentration to a region of lower concentration, with a magnitude that is proportional to the concentration

gradient. This is a first order rate process as it depends on the concentration.

$$J = -D\frac{dc}{dx}$$

where, J is the amount of drug passing perpendicularly through a unit surface area per time, D is the diffusion coefficient, and dc/dx is the concentration gradient. The negative sign suggests that diffusion occurs in the direction opposite to the increasing concentration i.e., it is the opposite of the concentration gradient.

Diffusion coefficient is proportional to the squared velocity of the diffusing particles, which depends on the temperature and viscosity of the system, and the size of the drug particles according to the Stokes-Einstein relation.

1.1.2 Fick's Second Law of Diffusion

Fick's second law is used for unsteady state situations, i.e., when we wish to predict how drug concentration changes with time. This law is valid when the amount of initial drug per unit volume is smaller than the dimensional solubility of drug particle. It predicts the drug concentration change with time during the diffusion process. This law is based on the assumptions that the entire drug dissolves during diffusion process, but that does not apply in the real situations, there are always some drug particles left behind. It says that, the rate of change in drug concentration in a volume within the diffusional field is proportional to the rate of change in spatial concentration gradient at that point. The diffusion coefficient is represented as:

$$\frac{dc}{dt} = D\frac{d^2C}{dx^2}$$

Thus, it states that the change in concentration with time in a particular region is proportional to the change in concentration gradient at that point. The concentration gradient is greatest at the beginning, as the drug amount in the matrix is at maximum at the beginning and then decreases with the time as the drug diffuses from the system.

1.2 Designing of Diffusion Controlled Matrix

Diffusion controlled systems are characterized by diffusion rate dependent drug release through an inert insoluble polymeric barrier.

Examples of diffusion controlled solid dosage forms are single-unit tablets, mini-tablets in capsules and particulates systems like microspheres or beads. In general, the methods used for the tablet manufacture include dry granulation, wet granulation, direct compression, and thermoplastic pelletizing (e.g., high shear, melt-extrusion, spray-congealing). The processes for producing spherical particulate systems cover spray-granulation or spray-drying, spray-congealing, extrusion-spheronization, solvent evaporation and emulsification. The nature of coating substrate (e.g., size, tensile strength, etc.,) is an important factor which needs consideration while selecting coating technique such as pan coater or fluidized bed coater. Generally, use of conventional manufacturing processes and equipment is preferred. When a more complex process is required (e.g., multilayered tablets, compression coating, mixed beads, or minitablets), emphasis should be placed on increased process and product understanding throughout the development lifecycle to ensure successful development from lab scale to commercial scale. During the product development, an understanding of drug release mechanism and key properties of the rate controlling materials is important to assure batch-to-batch consistency. It is well known that, the polymers have inherently higher variability in physicochemical properties. Thus, it is important to understand the structural multifariousness and potential impact on product performance due to the polymers used. The same compendial grade of materials from different manufacturers/ source may influence the product performance due to the variation in its chemical properties. In general, it is usually recommended to select a synthetic or semi-synthetic polymer such as hydroxypropyl methylcellulose (HPMC) over a natural polymer (e.g., alginate) because the chemistry and properties of the natural polymers are often influenced by a number of factors (e.g., source, geographical area, etc.,) that are difficult to control.

The process of drug diffusion depends on the nature and type of the drug, polymer and dissolution medium used in the study. The drug dissolution from a spherical molecule can be explained using Stokes-Einstein equation ($D = kBT/6\pi a\eta$), where kB is the Boltzmann's constant, T is the absolute temperature in Kelvin, a is the molecule's radius, and η is the solvent viscosity.

This equation confirms that the large molecules diffuse more slowly than small ones and the diffusion process decreased with an increase in the viscosity of liquids. The factor kBT in Stokes-Einstein equation accounts for the Brownian motion of molecules caused by thermal

agitation. In a polymeric system, the flow of polymer matrix is not like a liquid, and thus, the viscosity is not a correct parameter to predict diffusion of drug molecules.

The drug release from hydrophilic matrix after oral administration is based on diffusion of the drug through the hydrated polymer layer on the matrix surface (Paul & McSpadden, 1976). The molecules undergo collisions with each other, and results in thermal or Brownian motion. The theory of random walks shows that the average distance (root mean squared) that molecules travel by diffusion is proportional to the square root of time, i.e., average distance travelled $\sim \sqrt{Dt}$, where D is diffusion coefficient and t is time, a measure of the molecule's mobility in the medium.

The process of drug diffusion is a consequence of constant thermal movement of molecules, which results in a net transfer of drug molecules from a region of higher concentration to a region of lower concentration. The rate of diffusion from a matrix system is dependent on temperature, size, mass, and the viscosity of the microenvironment. Molecular movement of drug molecules increases with increase in temperature of the system leading to a higher average kinetic energy of the system (Lee, 1980).

$$\text{Kinetic energy (E)} = \frac{\text{Boltzmann's constant (k)} - \text{Temperature (T)}}{2}$$

$$= \frac{\text{Mass (m)} \times \text{Velocity (v)}}{2}$$

This equation shows that, an increase in temperature is exponentially correlated to velocity (v^2). Mass is also an important factor in the drug diffusion process. At a given temperature, mass of the molecule is inversely proportional to the velocity. The slower velocity of larger molecules is due to the more interaction of such molecules with the surrounding environment, which leads to slow particle diffusion. The environment viscosity also affects the diffusion process, since the rate of molecular movement is associated with the viscosity of the environment. In the case of a highly soluble drug, this may cause an initial burst release due to the presence of the drug on the matrix surface. Highly viscous gel layer thickness increases with time at the matrix surface due to the dissolution solvent permeation into the core of the matrix, which provides a diffusion barrier to drug release. The behaviour of such a gel layer is important in describing the release kinetics. After a certain time period

this swelling of the polymer layer stops due to complete hydration of the matrix. At this stage, the polymer chains become completely relaxed and the gel layer cannot be maintained and leads to disentanglement and erosion of the matrix surface. At this stage a sharp change occurs in the rheological behaviour of the gel layer. This suggests that the polymer-polymer and polymer-solvent interactions are important in controlling the gel network and erosion.

1.2.1 Classification of Diffusion Controlled Drug Delivery Systems

The drug release from a porous polymeric controlled release system, following diffusional release, occurs primarily through the network of wet pores created by solid drug particles that are loaded in the polymer matrix. Based on the principle of drug diffusion, controlled release systems can be classified either as a reservoir system or as a matrix system. In case of nonporous systems, the drug release is controlled by the drug solubility in the polymer matrix and by the drug diffusivity through polymer matrix. Whereas, in case of porous matrix, drug solubility and polymer network tortuosity affect drug release. In addition, drug loading also influences the release profile, since high loading can complicate the release mechanism because of formation of more cavities due to the release of more drug at higher drug concentration. Thus, the formation of more porous matrix may lead to increased rates of drug release. In monolithic systems, the drug is dissolved or dispersed within a matrix system, depending on its solubility and the drug release kinetics depends on drug solubility. If the drug level in the polymer matrix is below its solubility limit, it can be dissolved in a polymer matrix, and if, it is present above its solubility limit, it is dispersed. For such systems, it is assumed that the dissolution rate of the drug is slower compared to the diffusion rate of the drug. The drug release from diffusion controlled reservoir/matrix systems requires various assumptions such as: the drug diffusion coefficient in a particular medium must be constant, there should be a pseudo-steady state during drug release from these systems, the dissolution of solid drug must occur prior to the drug release.

1.2.2 Reservoir Diffusion Systems

The basic application of these systems is to control the release of water-soluble drugs surrounded by an insoluble polymer membrane. Microencuplation of drug or other particles and press coating of tablets exemplifies reservoir type devices. A porous membrane is produced by

adding soluble or leachable additive like water-soluble polymer, plasticizer etc., which resist drug diffusion at a predetermined rate upon contact with aqueous dissolution medium. The drug diffusion from reservoir device follows Fick's second law (unsteady-state conditions, concentration dependent flux). In case, the device contains dissolved drug, the process of drug release follows first order kinetics. It means, in such situation, the rate of release decreases exponentially with time as the concentration of the drug within the device decreases. In case, the device contains drug in the form of saturated suspension, the process of drug release follows zero order kinetics. Thus, the driving force for drug release is kept constant until the device is no longer saturated.

Drug release from the reservoir into external solution takes place in three steps:

(i) dissolution of drug in polymer;
(ii) diffusion of drug across the polymer membrane
(iii) dissolution of the drug into external phase.

The drug release from these systems is based on various assumptions such as there is no bulk flow (no convection), no generation/consumption of drug, the drug is diluted within the material, and drug release is controlled by the thickness and composition of surrounding membrane. The drug release rate depends on drug solubility, film thickness, and pore characteristics. These systems are effective at achieving zero-order, or constant drug delivery. However, there is a risk of significant burst release due to the accidental dose dumping, which may occur if the controlling membrane ruptures. The burst release effect has been observed in membrane reservoir systems after storage for specified time duration. When placed in a release medium, the drug diffused to the surface of the membrane is released immediately, causing a burst effect. The amount of drug released with an initial burst, M_t, from these systems is estimated by:

$$M_t = \frac{Dc_0}{1}\left(1 + \frac{l^2}{6D}\right)$$

where D is the drug diffusion coefficient, C_0 is the drug concentration on the inside of the membrane, and l is the membrane thickness, with a given burst of $C_0 l/6$, but the release profile during burst stage ($t > 0$) was not predictable. In order to maintain a constant release rate, the drug

concentration difference must remain constant. This can be achieved by placing drug at the centre of the matrix.

The drug solubility in polymer and in dissolution media based on interfacial partitioning can be expressed using following equation:

Partition coefficient of the drug molecule from polymer to solution (K)

$$= \frac{\text{Solubility of drug insolution phase } (C_s)}{\text{Solubility of drug insolution phase } (C_p)}$$

With the above assumptions, the cumulative amount of drug released (Q) from a diffusion-controlled reservoir type drug delivery system with a unit surface area can be depicted as:

$$Q = \frac{C_p K D_d D_m}{K D_d h_m + D_m h_d} - \frac{D_d D_m}{K D_d h_m + D_m h_d} \int_0^t C_{b(t)} d_t$$

where D_m is diffusivity of the drug in a polymer membrane having thickness h_m, D_d is diffusivity of hydrodynamic diffusion layer with thickness h_d, C_b is concentration of drug in reservoir, and t is time.

Under a perfect sink condition, $C_{b(t)} \cong 0$ or $C_s >> C_{b(t)}$, above equation reduced to

$$Q = \frac{C_p K D_d D_m}{K D_d h_m + D_m h_d} t$$

This shows that drug release can be a constant, with the rate of drug release being

$$\frac{Q}{t} = \frac{C_p K D_d D_m}{K D_d h_m + D_m h_d}$$

The rate of drug release depends on the polymer membrane layer or hydrodynamic diffusion layer. If, the release of drug is dependent on polymer membrane layer, in such case, $KD_d h_m >> D_m h_d$, and above equation becomes:

$$\frac{Q}{t} = \frac{C_p D_m}{h_m}$$

This shows that the rate of drug release is directly proportional to its solubility and inversely proportional to the polymer membrane thickness.

Transdermal delivery system is a typical example of the reservoir system. It consists of a backing layer, a rate-limiting membrane, a protective liner, and a drug reservoir compartment. The drug release from reservoir compartment is controlled through a rate-controlling polymer membrane. The drug release from such systems can be varied by selecting a proper polymer at different concentrations. The first transdermal system for systemic delivery, a three-day patch that delivers scopolamine to treat motion sickness, was approved in the United States in 1979.

Ocusert® is a commercially available reservoir system which delivers Pilocarpine to treat glaucoma. It is placed in the lower eye lid to administer drug for one week duration. This product was not successful due to patient compliance, as patients felt more comfortable using the regular drops compared to placing a foreign object in the eye. These devices are five times more expensive than regular drops (Malcolm *et al*., 2012).

Norplant® is another commercially available reservoir system consisting of 6 silicone rods containing 36 mg of levonorgestrel dissolved in the polymeric matrix. Norplant® is implanted under the upper arm skin. These systems are able to delivers hormone for up to five years (Malcolm *et al*., 2012). Currently this has been discontinued from the market due to multiple lawsuits in the USA.

1.2.3 Matrix Diffusion Systems

A matrix system, described as monolithic device, is designed by homogenous dispersion or dissolution of solid drug in an inert polymeric mix. These systems are favoured over other systems for their simplicity, low manufacturing costs, and lack of accidental dose dumping. These systems are easier to produce than the reservoir systems and can deliver high molecular weight drugs. The release property of the device depends upon the porous or nonporous nature of the matrix. Diffusional release of the drug is normally governed by Fick's first and second laws.

Mathematically, the rate of drug release in diffusion-controlled matrix systems can be described by Fick's first law of diffusion, which is expressed as:

$$J = -D\frac{dC}{dX}$$

where J is diffusion flux, D is the diffusivity of drug molecule, and dC/dX is concentration gradient of the drug molecule across diffusional barrier with thickness dX.

The drug release from a monolithic porous system is Fickian diffusion based on Fick's second law. Fick's second law describes how the concentration (c) within the diffusion volume changes with respect to time.

$$\frac{dC}{dX} = D.\Delta C$$

In such systems, the release rate is proportional to the square root of time and the release rate is dependent on the diffusion length. For the first 60% of released drug, the release corresponds to the early time approximation of Fick's second law, which is expressed as:

$$\frac{dM_t}{dt} = \sqrt{2M_0 \frac{D}{\pi l^2 t}}$$

where l is the thickness of a slab, M_o is the amount of drug dissolved, and M_t is the amount released at time t.

The release kinetics of diffusion controlled systems follows first order kinetics according to the following equation:

$$\frac{dM_t}{dt} = \sqrt{\frac{8DM_0}{l^2} \exp \frac{\pi^2 Dt}{l^2}}$$

Thus, a first order linear release profile is obtained for a drug releasing from a porous polymeric matrix. A simple mathematical model (Higuchi's model) is applied for the examination of drug release from a spherical system or a planar surface following diffusional release mechanism. For matrix systems, because of the changing thickness of the depletion zone, release kinetics is a function of the square root of time. Higuchi described the drug release from an insoluble homogeneous planar matrix system as a square root of time dependent process based on Fickian diffusion:

$$Q = \sqrt{(2C - C_s)\ DtC_s}$$

where Q is the amount of drug released at time t, D is the diffusitivity of the drug, C is the drug initial drug concentration, and C_s is the solubility of the drug in the matrix.

1.2.4 Factors Affecting Drug Release Rate from Monolithic Matrix Systems

1. Initial drug loading, solubility and dissolution rate
2. Boundary conditions

(i) The sink condition
(ii) Stagnant layers and external mass-transfer resistances
(iii) Dissolution media of finite volume

3. Drug and matrix diffusion coefficients
4. Drug molecular weight and size
5. Matrix pore size
6. Tortuosity of interconnecting channels within matrix
7. Matrix swelling
8. Osmotic pressure gradients
9. Ionic exchanges
10. Local electromagnetic force fields
11. Matrix erosion and drug solubility.

1.3 Designing of Dissolution Controlled Matrix

The dissolution process involves two basic steps, containing, and initial separation of drug molecules from the solid surface to the adjacent interface of the dissolution medium followed by their diffusion from the interface into the bulk dissolution medium. It is possible to develop a controlled release system of highly water soluble drug by decreasing the drug dissolution rate by coating the drug with slowly dissolving materials, or by incorporating it into tablet with a slowly dissolving carrier. Encapsulated dissolution systems can be prepared either by coating particles or granules of drug with varying thickness of slowly soluble polymers, or by micro-encapsulation. These coated particles can be compressed into tablets called as SPACETABS or placed in capsules as in SPANSULES. After the dissolution or erosion of the coating, drug molecules become available for absorption. Release of the drug at a predetermined time is accomplished by controlling the thickness of coating. In Spansule®, drug molecules are enclosed in beads of varying thickness to control the time and amount of drug release (Shen *et al*., 2003). The encapsulated particles with thin coatings will dissolve and release the drug first, while a thicker coating will take longer to dissolve and will release the drug at a later time. Coating-controlled delivery systems can also be designed to prevent the degradation of the drug in the acidic environment of the stomach. Such systems are generally referred as enteric-coated systems. Most of the formulations relying on dissolution to release the drug fall into three categories:

1. Encapsulated dissolution systems
2. Matrix dissolution systems
3. Multi-layer matrix tablet

Dissolution of drug from dosage form occurs till the surrounding dissolution medium is not saturated. The process of drug dissolution involves two steps. In the first, solid dissociate from the matrix surface and surround itself with dissolution medium. In second step, the solvated drug diffuses away from the matrix surface. The first step is more rapid than the second step, unless the drug is highly insoluble.

The fundamental principle for surface action phenomenon of drug dissolution in a liquid media was proposed by Noyes-Whitney in 1897. According to the Noyes–Whitney equation, the amount dissolved per unit area per unit time i.e., rate of drug dissolution (dC/dt) can be expressed as:

$$\frac{dC}{dt} = \frac{DA}{h\ (C_0 - C_t)}$$

where D is the diffusion coefficient of drug in diffusion layer, h is thickness of diffusion layer, A is surface area of drug particles, C_0 is saturation concentration of the drug in diffusion layer, C_t is the concentration of drug in bulk fluid at time t.

The rate of drug dissolution is directly proportional to the surface area of the drug particle. When C_t is less than 15% of the saturated solubility, C_t has a negligible influence on the dissolution rate of the solid. Under such conditions, the dissolution of the solid is said to be occurring under sink conditions. In general, the surface area (A) and thickness (h) of hydrodynamic diffusion layer are not constant except when the quantity of material present exceeds the saturation solubility, or initially, when only small quantities of drugs have dissolved. Factors affecting dissolution kinetics include particle size, solubility of polymers, viscosity of the hydrated polymer, diffusion coefficient (diffusivity), hydrodynamics of the stirring solvent, and diffusion of dissolved drug molecules through the hydrated polymer layer, and pH of the dissolution medium for enteric-coated controlled release systems.

In case of dissolution of powdered drug, a cube-root relationship is observed between the amount of remaining solid mass and time. This relationship is known as Hixson-Crowell cube-root law and represented by the equation:

$$W_0^{1/3} - W_t^{1/3} = \kappa t$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, Wt is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa); a constant incorporating the surface-volume relation. For dissolution of solid particles, this law assumes that the thickness of the diffusion layer is constant during the dissolution process; however this is not necessarily true.

In case of system coated with water soluble polymers, the first step of dissolution is hydration of polymer layer followed by dissolution (disentanglement) of the hydrated polymer. Esters of phthalic acid (weak acids containing carboxyl groups) are commonly used as enteric coating polymer. These polymers contain carboxylic acid groups which are un-ionized at gastric pH (pH 1.2 to 4.8) but become ionizedat intestinal pH (pH 6-7.5). The dissolution of enteric coating in alkaline pH is depended upon the ionization of polymers utilized. Enteric coating disrupt at higher pH due to the repelling effect of ionized polymers. Rapid dissolution of enteric coated systems requires higher pKa values of polymers compared to pH values of the dissolution media.

1.4 Kinetic Modeling on Drug Release from Diffusion and Dissolution Controlled Drug Delivery Systems

Kinetic modeling of drug release from diffusion and dissolution controlled drug delivery systems is helpful to speed up the process of product development and to better understand the mechanisms that are governing drug release from the developed delivery systems.

1.4.1 Zero Order Model

The process that takes place at a constant rate, independent of drug concentration is called as zero order kinetics. It means that, the rate of process cannot be increased with an increase in drug concentration. This ideal delivery is particularly important in certain classes of drugs, such as, antibiotic, ant-diabetic, anti-hypertensive, antidepressants etc.

Mathematically, the process of drug dissolution from dosage forms that do not disaggregate and allow a slow drug release (assuming that the area does not change and no equilibrium conditions are obtained) can be represented by the equation:

$$Q_t = Q_0 - K_0 t$$

where, Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release rate constant. The rate constant for zero order process is expressed in terms of mg/min.

To study the release kinetics, data obtained from *in vitro* drug release studies are plotted as the cumulative amount of drug released against time. This plot yields a straight line whose slope is $-K_0$. The half life of the drug following zero order kinetics can be calculated as $0.5\ Q_0/K_0$. This indicates that, the half life of drug depends on initial drug concentration. This model can be applied for the determination of drug release kinetics from transdermal systems, IV infusion and matrix tablets containing low soluble drugs (Varelas *et al*., 1995).

1.4.2 First Order Model

This model was first proposed by Gibaldi and Feldman in 1967 to describe the process of absorption and elimination of drugs (Gibaldi & Feldman 1967). However, theoretical conceptualization of this model is a difficult task. The release of the drug which followed first order kinetics can be expressed by the equation:

$$\frac{dC}{dt} = -Kc$$

where K is the first order rate constant expressed in units of $time^{-1}$.

Above equation can be expressed as:

$$\log C = \log C_0 - \frac{K_t}{2.303}$$

where C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The above equation shows that, the first order processes are directly proportional to the drug concentration, it means, the rate of process increases linearly with an increase in drug concentration. The data obtained from the *in vitro* release study of a porous matrix system containing water soluble drug are plotted as log cumulative percentage of drug remaining against time which yield a straight line with a slope of – K/2.303. The rate constant for first order kinetics is expressed as min^{-1} or $hour^{-1}$. The half life of the drug following first order kinetics can be calculated as 0.693/K. This indicates that, the half life is concentration independent and it is constant. This model is

mainly applicable to determine the release kinetics of dosage form those containing water soluble drugs in a porous matrix (Mulye & Turco, 1995).

1.4.3 Higuchi Model

A square root time dependent diffusion controlled drug release process of water soluble drugs from a hydrophilic matrix or suspensions based on Fick's first law was described by Takeru Higuchi in 1961 (Higuchi, 1961). He divided the matrix into two regions. In one region (depletion zone) all drugs are dissolved and a concentration gradient exists, and in the other region solid and dissolved drug coexist, making the dissolved drug concentration constant. This model is based on various hypotheses, such as, the drug is equally spread in the matrix, diffusion is unidirectional due to the negligible edge effect; the drug concentration in the matrix is initially much higher than the solubility of the drug; the thickness of the dosage form is much larger than the size of the drug molecules; the swelling and dissolution of the matrix is negligible; the diffusivity of the drug is constant; and perfect sink conditions are attained (Higuchi, 1963).

Initially, this equation was valid only for planar matrix systems, and later it was modified to consider different geometrical shapes and matrix characteristics including porous structures. Following equation was obtained to study the dissolution from a planar system having a homogeneous matrix:

$$Q = \sqrt{(2C - C_s)DtC_s}$$

where Q is the amount of drug released at time t, C is the drug initial drug concentration, C_s is the drug solubility in the matrix media and D is the diffusivity of the drug molecules in the matrix.

Assuming that diffusion coefficient and other parameters remain constant during the release, the above equation reduces to:

$$Q = \sqrt{Kt}$$

Thus, for diffusion controlled release mechanism, a plot of cumulative percentage of drug released against the square root of time will result in a straight line. The linearity of the plots is confirmed by the calculation of correlation coefficient. The equation was derived under pseudo-steady state assumptions and cannot be applied to real controlled release systems. According to the Higuchi's model, the data obtained from

in vitro dissolution study are plotted as a cumulative percentage drug release against the square root of time (Awasthi & Kulkarni, 2014a). This relationship can be applied to depict the drug dissolution from several modified release pharmaceutical dosage forms, such as transdermal systems and matrix tablets containing water soluble drugs.

1.4.4 Peppas' Model

According to logarithmic form of Peppas' equation, the rate of drug release can be expressed as:

$$Q = Kt^n$$

the logarithmic form of the above equation is

$$\log Q = \log K + n \log t$$

where Q is the amount of drug released, 't' is the time and 'n' is the slope of the linear plot. If the value of n is less than or equal to 0.5, the mechanism of drug release is diffusion without swelling. If the value is greater than 0.5 and less than 1, the release through diffusion with swelling and if it is above 1, the release mechanism is anomalous diffusion, not confirming to any Fick's laws (non-Fickian)(Awasthi & Kulkarni, 2014a; Peppas, 1985; Ritger & Peppas, 1987a,b).

1.4.5 Krosmayer Peppas Model

(Korsmeyer et al. 1983) derived a semi-empirical model, which described the drug release from a polymeric system. According to the Korsmeyer-Peppas model, first 60% drug release data are fitted to find out the mechanism of drug release. This model is generally applied to analyze the drug release from a polymeric dosage form, where the release mechanism is not well recognized or when more than one type of release process could be involved (Peppas & Korsmeyer, 1986). To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release versus log time.

$$\frac{M_t}{M_\infty} = Kt^n$$

Where M_t / M_∞ is a fraction of drug released at time t, K is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices.

In case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super case II transport.

This model is based on following assumptions:

1. Drug release occurs in an one dimensional way.
2. The length to thickness ratio of system should not be less than 10.
3. The equation is applicable for small values of time (t) and the portion of release curve where $M_t/M_\infty < 0.6$ should only be used to determine the exponent n.

1.4.6 Hixson Crowell's Model

(Hixson and Crowell 1931) reported that the particles' regular area is proportional to the cube root of its volume. This model describes the drug release from systems where there is a change in surface area and diameter of delivery system, such as, particles or tablets. They derived the equation:

$$W_0^{1/3} - W_t^{1/3} = \kappa t$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface-volume relation.

The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as the cube root of drug percentage remaining in the matrix versus time. This expression applies to pharmaceutical dosage forms where the dissolution occurs in planes that are parallel to the drug surface. In case, if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time (Niebergall *et al*., 1963).

1.4.7 Selection of the Best Fit Model for Release Data

Based on the statistical treatments, determination of correlation coefficient 'r^2' is the most widely used method to assess the fit of the model equation. The model having r^2 values less than 1 but, closest to 1 is considered as best fit model. However, this approach can be applied only

when the parameters of the model equations are similar. But when the parameters of the comparing equations increased; an adjusted coefficient (r^2 adjusted) is used for selecting best fit model using following equation:

$$r^2_{adjusted} = 1 - \frac{n-1}{n-p}(1-r^2)$$

where, n is the number of dissolution data points and p is the number of parameters in the model. Hence, the best model is the one with the highest adjusted coefficient of determination. Similarly, other statistical tools like Analysis of Variance (ANOVA) and Multivariate analysis of variance (MANOVA) are used for the selection of best fit models (Costa & Lobo, 2001).

1.5 Design and Fabrication of Gastroretentive Dosage Forms

The goal in designing controlled release drug delivery system is to control the drug concentration in target tissue, reducing the number of administrations and to improve the efficacy of drugs. However, a controlled release dosage form offers limited advantages for drugs that have an absorption window in the stomach or solubility dependent absorption. In order to increase the bioavailability of this type of drug, the residence time of the controlled-release dosage form in the stomach needs to be prolonged (Streubel, 2006). Gastroretentive controlled drug delivery systems have found to produce more significant improvement in pharmacotherapy of drugs having narrow absorption window in the gastrointestinal tract. Several attempts have been made to improve the bioavailability of drugs by increasing the residence time of dosage form in the gastric region. Over the last two decades, numerous gastroretentive systems such as high density, floating, expandable, mucoadhesive or bioadhesive, magnetic, dual working systems and superporous systems have been designed to prolong the gastric retention time (Pawar *et al*., 2011). Fig. 1.2 describes localization mechanisms of the different gastroretentive dosage forms and Table. 1.1 presents list of marketed formulations based on gastric retention technology.

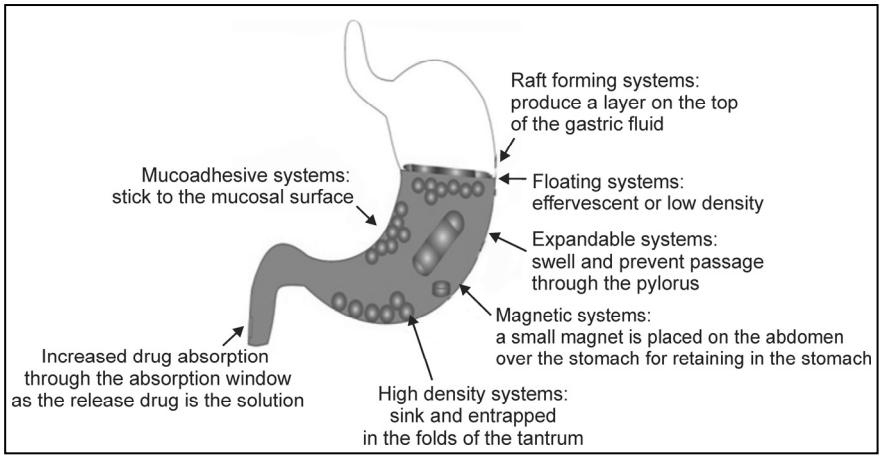

FIGURE 1.2 Localization mechanisms of the different gastroretentive dosage forms.

After administration, these systems remain in the stomach for a determined time period and can maintain the drug concentration at the target site. Gastric floating drug delivery system is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The major advantage of these systems is that the released drug will have whole surface area of stomach and small intestine for absorption. These systems are not suitable for those drugs which cause gastric lesions, such as non steroidal anti-inflammatory agents.

1.5.1 Gastrointestinal Motility

Two distinct patterns of gastrointestinal motility and secretion exist corresponding to the fasted and fed states. The fasted state is associated with various cyclic events which is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC). MMC is divided into four consecutive phases: phase I (basal phase) occurs for 40 to 60 min with rare contractions, phase II (preburst phase) lasts for 40 to 60 min with intermittent action potential and contractions, phase III (burst phase) occurs for 4 to 6 min with intense and regular contractions for short period, and phase IV lasts for 5 min; a transitional phase that occurs between phases III and I of two consecutive cycles. Due to intense waves of phase III, all the material is swept out of the stomach to the small intestine. Phase III waves are also known as the 'housekeeper' waves. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. The motor activity after meal ingestion is induced after 5-10 min and it persists as long as food remains in the stomach. The large

amount of food ingested is corresponds to the longer period of fed activity (2-6 h) with phasic contractions similar to Phase II of MMC (Takahashi, 2012).

1.5.2 Factors Affecting Gastric Retention

1. ***Density of the drug delivery system:*** Gastric retention time (GRT) is a function of buoyancy of dosage form which is dependent on the density of the system. Density of dosage form should be less than the gastric contents (Awasthi *et al*., 2010).
2. ***Size and shape of dosage form:*** Dosage form units with a diameter greater than 7.5 mm are reported to have an increased GRT. Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better retention at 24 h compared with other shapes (Timmermans & Moes, 1994).
3. ***Single or multiple unit dosage forms:*** Multiple unit formulations show more predictable release profile and insignificant impairing of formulation performance due to the failure of units. They allow co-administration of units with different release profiles and permit larger margin of safety against dosage form failure compared to single unit dosage forms (Newton, 2010).
4. ***Fed or unfed state of the stomach:*** Under fasting conditions, the gastric motility is characterized by periods of strong motor activity or MMC that occurs every 1.5 to 2 h. The MMC sweeps undigested material from the stomach. The GRT of the unit can be expected to very short when timing of formulation administration coincides with MMC (Mazer *et al*., 1988).
5. ***Nature of meal:*** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate.
6. ***Caloric content:*** GRT can be increased by 4 to 10 h with a meal having high proteins and fats content.
7. ***Frequency of feed:*** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal leading to low frequency of MMC.
8. ***Age:*** Elderly people, especially those over 70, have a significantly longer GRT (Mojaverian *et al*., 1988).

9. ***Posture:*** GRT can vary between supine and upright ambulatory states of the patient (Mojaverian *et al*., 1988).
10. ***Gender:*** Mean ambulatory GRT in males (3.4 ± 0.6 h) is less compared with their age and race matched female counterparts (4.6 ± 1.2 h), regardless of the weight, height and body surface (Mojaverian *et al*., 1988).

1.5.3 Formulation Approaches

Formulation approaches used for the development of gastroretentive systems are classified into the six categories based on formulation variables and mechanism of gastric retention. These systems have different principles of working and have their own merits and demerits.

1. High density systems
2. Swelling and expandable systems
3. Mucoadhesive or bioadhesive systems
4. Superporus hydrogel based systems
5. Magnetic systems
6. Floating systems

1.5.4 High Density Systems

The density of gastric content is close to the density of water (~1.004 g/cm^3), whereas the density of these systems, is about 3 g/cm^3. These systems are retained in the stomach due to high density, and are capable of withstanding its peristaltic movements. This phenomenon is confirmed by various clinical studies (Hejazi & Amiji, 2002; Timmermans & Moes, 1994). The manufacturing of high density systems is technically difficult with a large amount of drug, because weight of the matrix decreases progressively as the drug gets released. Thus, the duration of gastric retention also reduce. High density systems have not been significantly able to extend the gastric residence time (Rouge *et al*., 1998).

1.5.5 Swelling and Expandable Systems

The initial size of an ideal expandable system should be minimum possible to facilitate easy swallowing. Once the dosage form reaches stomach, the size of the dosage form should significantly increase rapidly and thus prevent premature passage through the pyloric sphincter. For these systems, some amount of gastric fluid in the stomach is must as the

swelling takes place due to the fluid absorption by the system. Superporous hydrogels can reduce this problem to a certain limit as they have high swelling capacity. The desired expansion can be achieved by swelling due to the osmosis or unfolding of polymeric chains. An expandable system based on unfolding mechanism has been reported for veterinary applications. The size of the expandable system needs to decrease after the complete drug release for easy evacuation from the stomach. The system should be designed in such a way that it gets eliminated from the body after completion of drug release. In terms of safety, these systems should not interfere with gastric motility, must be biodegradable, and must not cause any local damage to the gastric mucosa (Hou *et al*., 2003).

1.5.6 Mucoadhesive or Bioadhesive Systems

Adhesion of the delivery system to the stomach mucosal membrane is an attractive approach to prolong the gastric retention time of dosage form in the stomach. The gastric mucoadhesion of the dosage form may follow any of the mechanisms reported for mucoadhesion, such as absorption, diffusion, electron transfer, orwetting. The bioadhesion of polymers to the mucus membrane is achieved by the formation of electrostatic and hydrogen bonding at the mucus-polymer boundary. These formulations utilize materials such as, polyacrylic acids (Carbopol), chitosan, cholestyramine, dextrin, gliadin, HPMC, polyethylene glycol, sodium alginate, sucralfate, tragacanth, etc., which enables the device to adhere to the gastric mucosal wall. It has been established that the anionic polymers have better mucoadhesion property than neutral or cationic polymers (Huang *et al*., 2000). It seems that the mucoadhesive polymers are unable to effectively control gastrointestinal transit of the dosage form. It is very difficult to maintain effective mucoadhesion, due to continuous renewal of gastric mucosa, resulting in unpredictable adherence of delivery system to the gastric mucosa. These systems can cause local side-effects, such as gastric irritation, due to the prolonged contact of system with gastric mucosa (Chun *et al*., 2005).

1.5.7 Superporous Hydrogel based Systems

Hydrogels have been used in pharmaceutical products due to their biodegradable and biocompatible property. These are cross linked network of hydrophilic polymers that are insoluble in water. Hydrogels have the ability to swell by absorbing water or gastric fluid (Fig. 1.3). The rate of swelling of conventionally available hydrogels is very slow,

and hence, there are chances of premature evacuation of the delivery system through the pyloric sphincter. Therefore, such conventional hydrogels are commonly not preferred in the development of gastroretentive drug delivery systems. Superporous hydrogels had pore size >100 μm and swell very fast due to rapid water uptake, hence, superporous hydrogels are important in the development of gastroretentive drug delivery systems. Superporous hydrogels are water insoluble, thus, can retain their mechanical strength. Examples of commonly used materials for forming superporous hydrogels are poly (acrylamide-co-acrylic acid)/ polyethyleneimine polymer networks, polymerized vinyl monomers, or acrylate derivatives, sucrose and croscarmellose sodium (Qiu & Park, 2003).

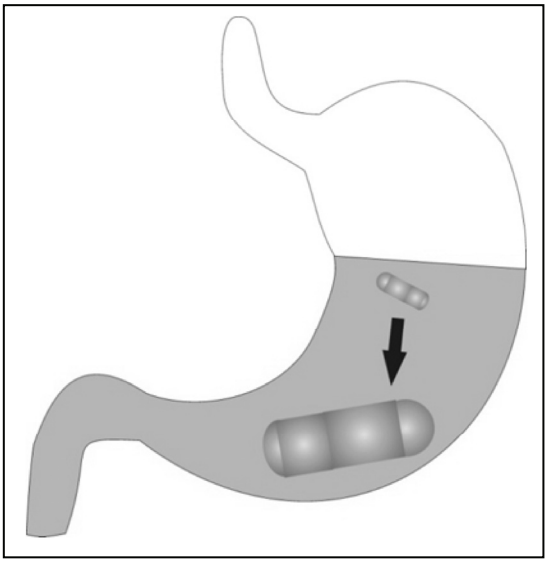

FIGURE 1.3 Expansion of a superporous hydrogels based gastroretentive system upon contact with gastric fluid.

1.5.8 Magnetic Systems

Magnetic systems contain a small internal magnet (iron powder) and an extracorporal magnet placed on the abdomen over the position of the stomach, which control the gastrointestinal transit of the dosage form. A number of human studies on gastroretention properties have been reported by many researchers based on magnetic systems. The images are taken by very sensitive bio-magnetic measurement equipments. The major drawback of these systems is that the effectiveness of the therapy depends on the position of the external magnet, which might compromise patient compliance. The prolonged retention of these systems in human

stomach has been proved by magnetic resonance imaging of the dosage forms (Groning *et al*., 1998).

1.5.9 Floating Drug Delivery Systems

These are low-density systems which float over the gastric fluids and thus increase the retention time at the site of drug absorption, particularly in the stomach. These delivery systems are formulated by the incorporation of carbonate or bicarbonate salts in the swellable polymer matrix. Here, the density of dosage form decrease due to the entrapment of carbon dioxide gas within the polymer matrix, which is responsible for buoyancy (Mouzam *et al*., 2011). These systems release the medicament in a controlled manner while the system floats over the gastric fluid, which results in increased bioavailability of the drug with reduced fluctuation in plasma concentration.

1.5.9.1 Classification of Floating Drug Delivery Systems

Floating systems can be classified based on the mechanism of buoyancy. Major classes of floating drug delivery systems are effervescent systems, noneffervescent systems, low density systems, and raft forming systems. The first category of floating systems is effervescent systems which are obtained by the incorporation of bicarbonate salt which is responsible for gas generation or by volatilization of an organic solvent which make hollow cavity. The other category is non-effervescent systems which are formulated by using gel-forming and highly swellable polymers.

1.5.9.2 Effervescent Systems

These systems are prepared by using swellable polymers such as methylcellulose and a gas forming agent like carbonate or bicarbonate salt with or without tartaric acid/citric acid. The coated resin beads containing bicarbonate are the most common systems prepared by this approach. In this system, the insoluble but permeable coating allows water to permeate through it, releasing carbon dioxide gas, causing the system to float when comes in contact with gastric environment. Other materials and approaches used are light mineral oils, mixture of cellulose derivatives and Carbopol along with $NaHCO_3$, polypropylene foam powder, mixture of alginate and bicarbonate salt, and systems based on ion exchange resin technology (Rubinstein & Friend, 1994).

1.5.9.3 Non-Effervescent Systems

These delivery systems are developed by using a high level of gel-forming, highly swellable polymers. HPMC is most commonly used for the preparation of non-effervescent floating systems, although agar, carrageenans, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), and sodium carboxymethycellulose (NaCMC) are also used. The penetration of fluid inside the device and consequent drug release is controlled due to the hydration of gel forming polymers and formation of gel barrier when comes in contact with the gastric fluid. The buoyancy of the dosage form depends on the density of swollen polymeric matrix, which can be reduced due to the entrapped air within the matrix (Nakamichi *et al*., 2001).

1.5.9.4 Hydrodynamically Balanced Systems

Hydrodynamically Balanced Systems (HBS) are able to prolong the retention time for a long period by maintaining their low apparent density due to the hydration of polymer and formation of gel barrier (Erni & Held 1987).

1.5.9.5 Low-Density Systems

The major drawback of floating systems based on the mechanism of gas generation is that they have a floating lag time. Due to this, the system may undergo premature evacuation. The system having density lower than the gastric fluid does not have this kind of problem. Floatation can also achieve by the volatilization of an organic solvent (e.g., dichloro-methane). These are particulate systems such as microspheres or microballoons. They are characteristically free flowing powders with a size less than 200 μm. In these systems, low density materials are used as drug carrier. A buoyant system can also be developed by using a fluid-filled globular shell that floats in the stomach. A drug-polymer solution is used for further coating of these systems. Finally, the product remains buoyant for a prolonged time period over the gastric content with a constant and controlled drug release (Sharma & Pawar, 2006). For easy administration and accurate dose, these systems can be compressed into fast disintegrating tablets.

1.5.9.6 Raft Forming Systems

These are boat like systems, which float over the gastric fluid in the form of a continuous layer which is known as raft. The raft forming systems involve the formulation of effervescent floating liquid with *in situ* gelling properties, which has been assessed for sustaining drug delivery and

targeting. The raft floats on the gastric fluid because it has bulk density less than the gastric fluid created by the liberation of carbon dioxide gas and act as a barrier to prevent the gastric reflux. When the system floats on the gastric fluid, the drug is released slowly in a controlled manner. After complete release of the drug, the residual system is emptied from the stomach. Raft forming systems have received much attention for the delivery of antacids and drug delivery for the treatment of gastrointestinal infections and disorders. These systems are designed by using a polymer having gel forming property. Carbonate or bicarbonate salts are also used as co-excipients in the formulation of these systems. When the system comes in contact with the gastric content, it forms a viscous gel. The presence of bicarbonate salts is responsible for gas generation. The system floats due to the entrapment of carbon dioxide gas within the viscous gel. Antacids such as aluminium hydroxide and antibiotics such as amoxicillin can be good candidates for incorporation in these systems (Rajinikanth & Mishra, 2008).

The conceptualization of the raft forming systems depends on the physicochemical properties of the drug molecule and the diseased condition for which treatment is required. Physicochemical and pharmaceutical factors include molecular weight, lipophilicity, molecular charge, pH, gelation temperature, viscosity, osmolarity, and spreadability whereas physiological factors include membrane transport and pH of tissue fluid. To achieve desired gastric retention of the system, the dosage form must be able to satisfy the following criteria:

1. The drug should be released in a controlled manner from the system while maintaining buoyancy for a prolonged period of time.
2. The dosage form must be able to withstand the force exerted by peristaltic waves, constant contractions, grinding and churning moments in the stomach.
3. Dosage form should maintain specific gravity lower than gastric fluid (1.004–1.01 g/cm^3).
4. Easy to administer.
5. After complete release of drug, the device should be easily evacuated from the stomach.

Various mechanisms for raft formation which have been reported are summarized below (Hampson *et al*., 2005):

1.5.9.6.1 Raft Formation based on Chemical Mechanism

Here, ion sensitive polysaccharides such as carrageenan, gellan gum, pectin, and sodium alginate undergo phase transition in the presence of various ions such as K^+, Ca^+, Mg^+, and Na^+.

1.5.9.6.2 Raft Formation based on pH Dependent Gelling

In the development of such systems, various pH dependent polymers such as Carbopolor its derivatives, polyvinylacetal diethylaminoacetate, mixtures of poly (methacrylic acid) and poly(ethylene glycol) are used which organise into a *in situ* gel system (sol to gel) with respect to change in pH.

1.5.9.6.3 Raft Formation based on Temperature Dependent Gelling

This approach is based on the use of polymers which undergo temperature induced phase transition. Hydrogels such as pluronics [(poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide)] (PEO–PPOPEO Triblock), polymer networks of poly(acrylic acid) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate) are commonly used for the development of such systems. These hydrogels are liquid at room temperature (~25°C) and undergo gelation upon contact with body fluids (37 ± 2°C).

1.5.10 Advanced Technologies used to Develop Gastroretentive Systems

Various advanced approaches have been reported to increase the gastrointestinal transit time of the drug delivery systems in the stomach.

1.5.10.1 Intragastric Floating Gastrointestinal Drug Delivery Systems

These systems are composed of a drug reservoir encapsulated in a microporous compartment with apertures along its top and bottom surfaces. The walls of the drug reservoir compartment are properly sealed to avoid any direct contact of the undissolved drug with the mucosal surface. The intragastric floating can be achieved using low-density materials (e.g., fatty acids) and gas-forming agent. These systems can be prepared by simple ionotropic gelation method (Harrigan, 1977).

1.5.10.2 Inflatable Gastrointestinal Drug Delivery Devices

These devices are composed of an inflatable chamber containing a volatile liquid such as dichloromethane which gasified at 37°C to cause the chamber to inflate in the stomach. The inflatable chamber also contains a biodegradable polymer filament. These systems contain a copolymer of polyvinyl alcohol and polyethylene that gradually dissolves in the gastric fluid. Dissolution of this copolymer is responsible for the release of gas from the system after an extended period of time to permit the spontaneous ejection of the system from the stomach (Michaels, 1974).

1.5.10.3 Intragastric Osmotically Controlled Floating Drug Delivery Devices

These are hollow deformable polymeric capsule shells. The capsule is divided into two compartments separated by using a membrane that allows selective transport across it. The drug is enclosed in the inner reservoir, which is covered by an outer osmotically active compartment. The osmoticlally active compartment generally contains a volatile liquid such as dichloromethane that vaporizes at the body temperature. Vaporization of liquid increases the size of unit to inflate. The device contains a bioerodible plug that allows the vapours to escape from the device and bring it back to the original position after a prolonged period of time for easy removal from the body (Michaels *et al*., 1975). This device consists of two basic compartments:

1. ***Drug reservoir compartment:*** This compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice.
2. ***Osmotically active compartment:*** This compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, gastric fluid is continuously absorbed through the semipermeable membrane into the osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is created, which acts on the collapsible bag and, in turn, forces the drug reservoir compartment to reduce its volume and activate the release of a drug through the delivery orifice.

TABLE 1.1

List of marketed formulations based on gastric retention technology

Manufacturer	Dosage form	Brand Name	Active Drug	Technology
Hoffmann-LaRoche, USA	Capsule	Valrelease®	Diazepam	Floating capsule
Roche Products, USA	Capsule	Madopar®	Benserazide, Levodopa	HBS
Glaxosmithkline, India	Liquid	Liquid Gaviscon	Aluminium hydroxide, Magnesium carbonate	Effervescent floating preparation
Pierre Faber Drug, France	Liquid	Topalkan	Aluminium-magnesium antacid	Floating liquid alginate preparation
Ranbaxy, India	Colloidal gel	Conviron	Ferrous sulphate	Colloidal gel forming floating drug delivery system
Pharmacia, USA	Capsule	Cytotech	Misoprostol	Bilayer floating capsule
Ranbaxy, India	Tablet	Cifran OD	Ciprofloxacin	Gas-generating floating form
Pierre Fabre Drug, France	Liquid	Almagate float coat	Aluminium-magnesium antacid	Floating liquid formulation
Glaxosmithkline, Philadelphia	Effervescent floating form	Coreg CR	Carvedilol	Osmotic system
Bayer, USA	Tablet	Cipro XR	Ciprofloxacin hydrochloride and betaine	Erodible matrix based system
Sun Pharma, India	Tablet	Baclofen GRS	Baclofen	Coated multi-layer floating & swelling system
Sun Pharma, India	Tablet	Prazopress XL	Prazosin HCl	Effervescent and swelling-based floating system
Ranbaxy, India	Tablet	Zanocin OD	Ofloxacin	Effervescent floating system
Ranbaxy, India	Tablet	Riomet OD	Metformine HCl	Effervescent floating system
Depomed, USA	AcuForm	ProQuin XR	Ciprofloxacin	Polymer-based swelling technology.
Depomed, USA	AcuForm	Glumetza	Metformin HCl	Polymer-based swelling technology
Depomed, USA	AcuForm	Metformin GR	Metformin HCl	Polymer-based swelling technology

TABLE 1.1 ***Contd...***

Manufacturer	Dosage form	Brand Name	Active Drug	Technology
Galenix, France	Tablet	Metformin HCl LP	Metformin HCl	Minextab Floating
Galenix, France	Tablet	Cafeclor LP	Cefaclor	Minextab Floating
Galenix, France	Tablet	Tramadol LP	Tramadol	Minextab Floating
Sato Pharma, Japan	Tablet	Inon Ace Tablets	Siméthicone	Foam based floating system
Depomed, USA	AcuForm	Gabapentin GR	Gabapentin	Polymer-based swelling technology

1.5.11 Evaluation of Gastroretentive Drug Delivery Systems

In today's world, the quality product is a key strategic factor to meet the global regularity requirements for better realization of organizational goals such as better customer care and increased profitability. In recent years, the quality control measurements have received much attention of researchers from the academia and industries. The quality product can be obtained by a critical product evaluation process. In this respect, the evaluation should start during the preformulation stage and continued till the finished product is delivered. The preformulation studies focus on those physiochemical properties of the formulation ingredients that affect the drug performance and development of an efficacious dosage form. A thorough understanding of these properties, ultimately provide a rationale for formulation design. Drug identification test and drug-exicipients compatibility studies are done in this phase to provide a useful support in the development of dosage forms. The preformulation studies includes following tests:

1. Drug identification tests such as solubility, melting point, physical appearance etc.
2. Fourier transform infrared spectroscopy for drug identification and to investigate the possible interaction between drug and excipients.
3. Differential scanning calorimetry to examine the thermal behavior of drug alone or in combination with excipients.
4. X-ray diffraction studies to examine the physical state (amorphous or crystalline) of drug alone or in combination with excipients.

1.5.11.1 *In vitro* Evaluation

The density of dosage form is a major factor affecting the performance of such delivery systems, thus it is an important parameter to be evaluated during product development. To float on the gastric fluid, a system should have a density lower than the gastric fluid (~1.004 g/cm^3). True density can be determined using liquid displacement or photographic counting method. The percentage buoyancy (buoyancy lag time and buoyancy duration) can be determined by taking a predetermined amount of dosage form in 100 ml of suitable medium such as 0.1 N hydrochloric acid (pH 1.2). In case of multiparticulate systems, floated and settled particles are collected separately after predetermined time intervals. The fractions (floating and settled) are weighed and the buoyancy can be determined using following formula:

$$\text{Buoyancy (\%)} = \frac{\text{Weight of floating units}}{\text{Weight of floating units + Weight of settled units}} \times 100$$

As the morphology of the system has an influence on the drug encapsulation and drug release behaviour, the detailed observations of surface and cross-sectional characters of the micro-particles could be estimated by scanning electron microscope.

The percentage encapsulation (in the case of multiparticulate systems) is determined by suspending the powered microparticles in a suitable medium. After suitable time period, filtrate is analyzed for drug content using an analytical technique after suitable dilution. The percentage drug encapsulation can be determined by dividing the actual amount of drug present in the microparticles to theoretical amount of drug added to the formulation.

In vitro drug release from gastroretentive systems is generally performed in simulated gastric fluid at 37°C. Determination of drug release from the system at slightly higher pH, such as phosphate buffer pH 6.8, is also recommended due to the variation in gastric pH based on fasting or fed conditions. Dissolution tests generally are performed using USP II dissolution apparatus. USP 28 states ‘‘the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started’’. A small, loose piece of non-reactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float. It is described that the drug release rate is reduced when helical wire is used. This limitation can be overcome by the method reported by (Soppimath et al., 2001). Briefly, the floating drug delivery

system is fully submerged under a ring or mesh assembly. Recently, a custom-built stomach model has been reported for simultaneous depiction of buoyancy and drug release profiles (Eberle *et al*., 2014).

1.5.11.2 *In vivo* Evaluation

1.5.11.2.1 γ-Scintigraphy

In vivo buoyancy behaviour of gastroretentive systems can be examined using γ-scintigraphic technique. This technique is based on the incorporation of a radioisotope (such as 99 mTc-DTPA) within the dosage form. The radioisotope labelled formulation is administered to the suitable animals or human volunteers. Major draw-backs of this technique are ionization radiations, limited topographic information, low resolution, and high cost (Goole *et al*., 2008; Wilding *et al*., 2001).

1.5.11.2.2 Radiology

Radiology is a simplest technique used for estimation of *in vivo* gastroretention. However, this technique has not gained popularity due to exposure to X-rays. Radiographs are taken at various periodic time intervals after administration of the dosage form (Baumgartner *et al*., 2000).

1.5.11.2.3 Gastroscopy

Optic-fibers and a video camera are used for visual observation of dosage form in the stomach. Poor results may be obtained due to the presence of food in the stomach.

1.5.11.2.4 Ultrasonography

Ultrasonic waves are used to produce images of body structures. The waves travel through tissues and are reflected back where density differs. The reflected echoes are received by an electronic apparatus that measures their intensity level and the position of the tissue reflecting them. The results can be displayed as images or as a moving picture (Hendee, 1994).

1.5.11.2.5 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a non-invasive technology uses magnetic field, radio frequency pulses, and a computer to produce a detailed image of the buoyant formulation during *in vivo* conditions. This technique does not use ionization radiation as is observed with

γ-scintigraphy. Harmless paramagnetic and supra-magnetic imaging contrast agents are applied to obtain better results (Dorozynski *et al*., 2007).

1.5.11.2.6 Pharmacokinetics

These investigations involve analysis of blood samples at specified time intervals after dose administration. Pharmacokinetic parameters including maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}) and area under the curve (AUC) are investigated to assess the *in vivo* performance of these drug delivery systems.

1.5.12 Future Recommendations

The expected gastric retention, especially with low calories or fasted conditions is compromised. To provide evidence that a gastroretentive technology actually works, development and *in vivo* testing of the system should be carried out by considering following parameters (Awasthi and Kulkarni, 2014b):

1. The size, shape and surface morphology of dosage form should be monitored. The delivery system should not break into parts during the testing and should release the drug at a constant rate for prolonged period of time.
2. The buoyancy can be controlled either by controlling water penetration inside the delivery system or by modifying the swelling property of the system.
3. The analysis of the position of dosage form, to determine the buoyancy behaviour, should be done using an imaging technique.
4. The effect of caloric content of the meal should be carefully monitored during the product development. At least 6 h break should be given between two successive meals.

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