1.1 INTRODUCTION TO EXTENDED RELEASE MATRIX TABLET

During the last two decades there has been remarkable increase in interest in controlled release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of controlled release is also being applied to veterinary products.[1] An appropriately designed controlled-release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target tissue. Matrix tablets are an interesting option when developing an oral controlled release formulation. The use of polymers in controlling the release of drugs has become important in the formulation of pharmaceuticals.[2]

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at particular frequency. In most cases, the dosing intervals much shorter than the half life of the drug resulting in a number of **limitations associated with such a conventional dosage form** are as follows [3]:

- Poor patient compliance; increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- A typical peak plasma concentration time profile is obtained which makes attainment of steady state condition difficult.
- The unavoidable fluctuation in the drug concentration may lead to under medication or over medication as the steady state concentration values fall or rise beyond in the therapeutic range.
- The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs.

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in Figure 1 and 2 [4].

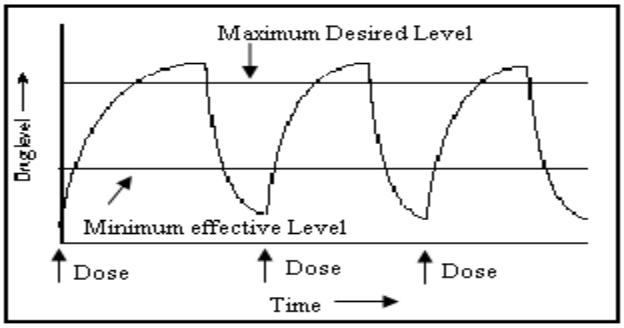


Figure 1: Drug levels in the blood with Conventional drug delivery systems [4]

The above problems can be overcome by the development of effective and safer use of existing drugs through concepts and technique of Controlled drug delivery system. The controlled drug delivery system is one, which delivers the drug at a predetermined rate, locally or systemically for a predetermined period of time.

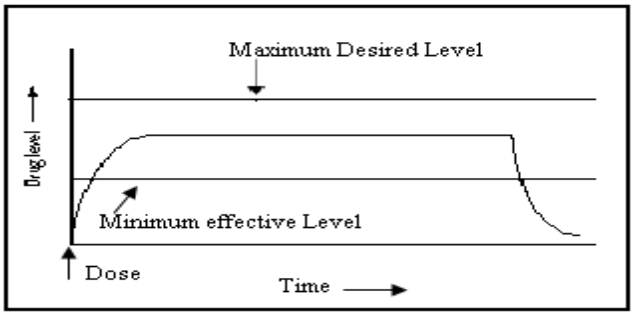


Figure 2: Drug levels in the blood with Controlled drug delivery systems [4]

The **advantages of Controlled drug delivery system** over the conventional dosage form are as follows [3]:

- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of dose administered.
- Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing.
- It is also good for patients to avoid the dosing at night time.

Disadvantages of Controlled drug delivery system [1]:

- ✓ Dose dumping.
- ✓ Less flexibility in accurate dose adjustment.
- ✓ Poor In Vitro – In Vivo correlation.
- ✓ Patient variation.

Criteria to be met by drug proposed to be formulated in controlled release dosage forms [1]:

a) Desirable half-life.
b) High therapeutic index
c) Small dose
d) Desirable absorption and solubility characteristics.
e) Desirable absorption window.
f) First past clearance.

a) Desirable half-life:
The half life of a drug is an index of its residence time in the body. Drug with elimination half life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to seven hours.

b) High therapeutic index:
Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities eg. Digitoxin.

c) Small dose:
If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty.

d) Desirable absorption and solubility characteristics:
Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.

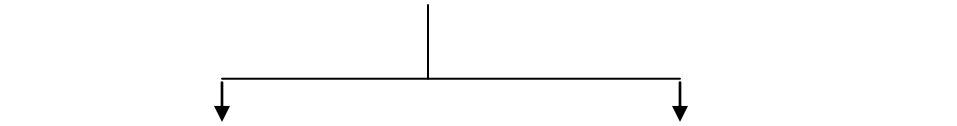
e) Desirable absorption window:
Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the ‘absorption window’. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable.

f) First pass clearance:
Delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms.

The term modified-release dosage form is used to describe products that alter the timing and rate of release of drug substance. A modified-release dosage form is defined "as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosages forms. The USP/NF presently recognizes several types of modified-release dosage forms as [2]:

1. **Oral Dosage Forms**
   -Modified release dosage forms
   -Extended release e.g. controlled release, sustained release and prolonged release
   -Delayed release e.g. enteric-coated tablets.
   -Site specific and receptor release:
2. **Intramuscular Dosage Forms**
   -Depot injections
   -Water-immiscible injections e.g. oils
3. **Subcutaneous Dosage Forms**
   -Implants
4. **Transdermal Delivery Systems**
   -Patches, creams, etc.
5. **Targeted Delivery Systems**

1.1.1 Classification of Extended/Controlled Release Systems:



1.1.1.1 Classification According to Release Pattern:

Types of Non-immediate Release Drug Delivery System (NRDDS)

The conventional dosage forms are immediate release type. Non-immediate release delivery systems may be divided conveniently into three categories: **[5, 6, 7, 8]**

- **Delayed release drug delivery systems:**
  - Repeat action Drug Delivery System
  - Timed release DDS
- **Sustained release drug delivery systems**
  - Controlled release DDS
  - Prolonged release DDS
- **Site specific and receptor release drug delivery systems**
  - Organ targeting DDS
  - Cellular targeting DDS
  - Sub cellular targeting DDS

[1] Extended release dosage forms:

It is defined as the one that allows at least a two fold reduction in the dosing frequency as compared to that of conventional dosage form.

[A] Controlled Action:

In this type of dosage forms it provides a prolonged duration of drug release with predictability and reproducibility of drug release kinetics. In this case, the rate of drug absorption is equal to the rate of drug removal from body.

[B] Sustained Action:

In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose.

[C] Prolonged Action:

These types of dosage form are designed in such a way that it release the drug over an extended period during which pharmacological response is obtained but does not necessarily maintain the constant blood level.

[2] Delayed release dosage forms:

It is defined as one that releases the drug at a time other than "immediately" after administration.

[3] Site specific and receptor release:

It refers to targeting of drug directly to a certain biological location.

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in a selected route of administration [1].

1.1.1.2 According to Technology:

1.1.1.2.1 Monolithic Systems (Matrix System):

Monolithic (matrix) devices are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrixes, the solubility in the sink solution within the particle's pore network and also the tortuosity of the network (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low loadings of drug, (0 to 5% W/V) the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loadings (5 to 10% W/V), the release mechanism will be complicated by the

presence of cavities formed near the surface of the device as the drug is lost: such cavities fill with fluid from the environment increasing the rate of release of the drug [9].

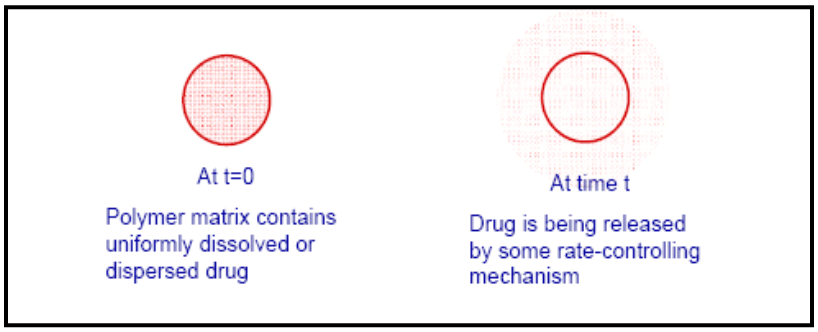


Figure 3: Rate Control: Matrix System [10]

1.1.1.2.2 Reservoir Systems

A typical approach to controlled release is to encapsulate or contain the drug entirely (*e.g.*, as a core within a polymer film or coat (*i.e.*, microcapsules or spray/pan coated cores). Kala H. et al. has reviewed the Film coating (with particular reference to polymers and their additives), whilst Arshady et al., has reviewed microencapsulation [11, 12, 13].

Fig. 4: Microbeads & Microtubes [14]

1.1.1.2.3 Chemically Controlled System [15]

- Bioerosion control
- Drug attached to a polymer backbone
- Drug in a biodegradable core
- Drug dispersed in a bioerodible matrix
  - Diffusion controlled
  - Erosion controlled
- Regulated Systems

  - Release varies with environment
  - Externally regulated
- Ultrasound
- Heat
- Magnetic
- Pumps
  - Self regulated
- pH changes
- Bonding to specific lectins
- Triggered devices

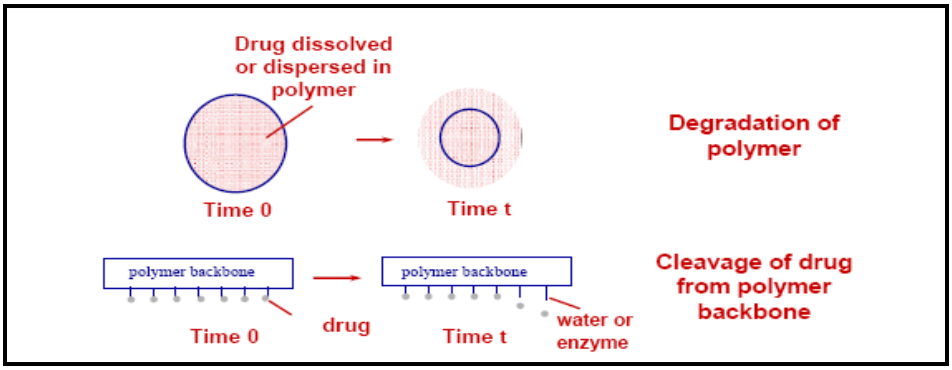


Fig. 5: Rate control: Chemical Reaction

1.1.2 Matrix Tablets [2]

These are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials.

Advantages of Matrix Tablets

·Easy to manufacture.

·Versatile, effective and low cost.

·Can be made to release high molecular weight compounds.

Disadvantages of the matrix systems:

·The remaining matrix must be removed after the drug has been released.

·The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front.

1.1.2.1 Mechanisms of Drug Release from Matrix Systems

The release of drug from controlled devices is via dissolution or diffusion or a combination of the two mechanisms.

1.1.2.1.1 Dissolution Controlled Systems

A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water-soluble [16]. This can be done by:

- Preparing an appropriate salt or derivative
- Coating the drug with a slowly dissolving material – encapsulation dissolution control
- Incorporating the drug into a tablet with a slowly dissolving carrier – matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time).

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. The dissolution process at steady-state is described by the Noyes-Whitney equation:

$$\frac{dC}{dt} = \frac{DA(C_s - C)}{h}$$

Where,

dC / dt = dissolution rate

D = the dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer D/h)

Co = saturation solubility of the solid

C = concentration of solute in the bulk solution

A = Surface area

h = Diffusion layer thickness

Equation predicts that the rate of release can be constant only if the following parameters are held constant:

- Surface area
- Diffusion coefficient
- Diffusion layer thickness
- Concentration difference.

These parameters, however, are not easily maintained constant, especially surface area, and this is the case for combination diffusion and dissolution systems[16].

1.1.2.1.2 Diffusion controlled systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier[17]. Usually, this barrier is an insoluble polymer. In general, two types or subclasses of diffusional systems are recognized: reservoir devices and matrix devices[16]. It is very common for the diffusion-controlled devices to exhibit a non-zero order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds[18].

Diffusion in matrix devices

In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows obviously that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix [16]. Derivation of the mathematical model to describe this system involves the following assumptions:

a. A pseudo-steady state is maintained during drug release.
b. The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
c. The diffusion coefficient of drug in the matrix remains constant (no change occurs in the characteristics of the polymer matrix [16].
d. The bathing solution provides sink conditions at all times.

e. No interaction occurs between the drug and the matrix.
f. The total amount of drug present per unit volume in the matrix is substantially greater than the saturation solubility of the drug per unit volume in the matrix (Excess solute is present) [19].
g. Only the diffusion process occurs [20].

• Diffusion controlled by **Fick's law.**

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

Where,

J = flux of the drug across a membrane in the direction of decreasing concentration,

D = Diffusion coefficient of the drug, and

dCm /dx = Change in the concentration of the drug in the membrane.

1.1.2.2 Classification of Matrix Tablets:

1.1.2.2.1 On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types.

1) Hydrophobic Matrices (Plastic matrices):

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles.

Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers.

The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2) Lipid Matrices:

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3) Hydrophilic Matrices:

The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in

the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

In a **hydrophilic matrix**, there are two competing mechanisms involved in the drug release: Fickian diffusional release and relaxation release. Diffusion is not the only pathway by which a drug is released from the matrix; the erosion of the matrix following polymer relaxation contributes to the overall release. The relative contribution of each component to the total release is primarily dependent on the properties of a given drug[21].

For example, the release of a sparingly soluble drug from hydrophilic matrices involves the simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion mechanism. As water penetrates into a glassy polymeric matrix, the polymer swells and its glass transition temperature is lowered. At the same time, the dissolved drug diffuses through this swollen rubbery region into the external releasing medium[22].

This type of diffusion and swelling does not generally follow a Fickian diffusion mechanism[20]. The semi-empirical equation to describe drug release behavior from hydrophilic matrix systems[22]

$$\mathbf{Q = k\, t^n}$$

Where,

Q = fraction of drug released in time t,

k = rate constant incorporating characteristics of the macromolecular network system and the drug

n = the diffusional exponent. It has been shown that the value of n is indicative of the drug release mechanism.

For n=0.5, drug release follows a Fickian diffusion mechanism that is driven by a chemical potential gradient. For n=1 drug release occurs via the relaxational transport that is associated with stresses and phase transition in hydrated polymers. For $0.5<n<1$ non-Fickian diffusion is often observed as a result of the contributions from diffusion and polymer erosion[20].

The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups:

a) Cellulose derivatives: methylcellulose 400 and 4000 cps; hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cps; and sodium carboxymethylcellulose.

b) Noncellulose natural or semisynthetic polymers: agar-agar; carob gum; alginates; molasses; polysaccharides of mannose and galactose; chitosan and modified starches.

c) Polymers of acrylic acid; corbopol 934, the most used variety.

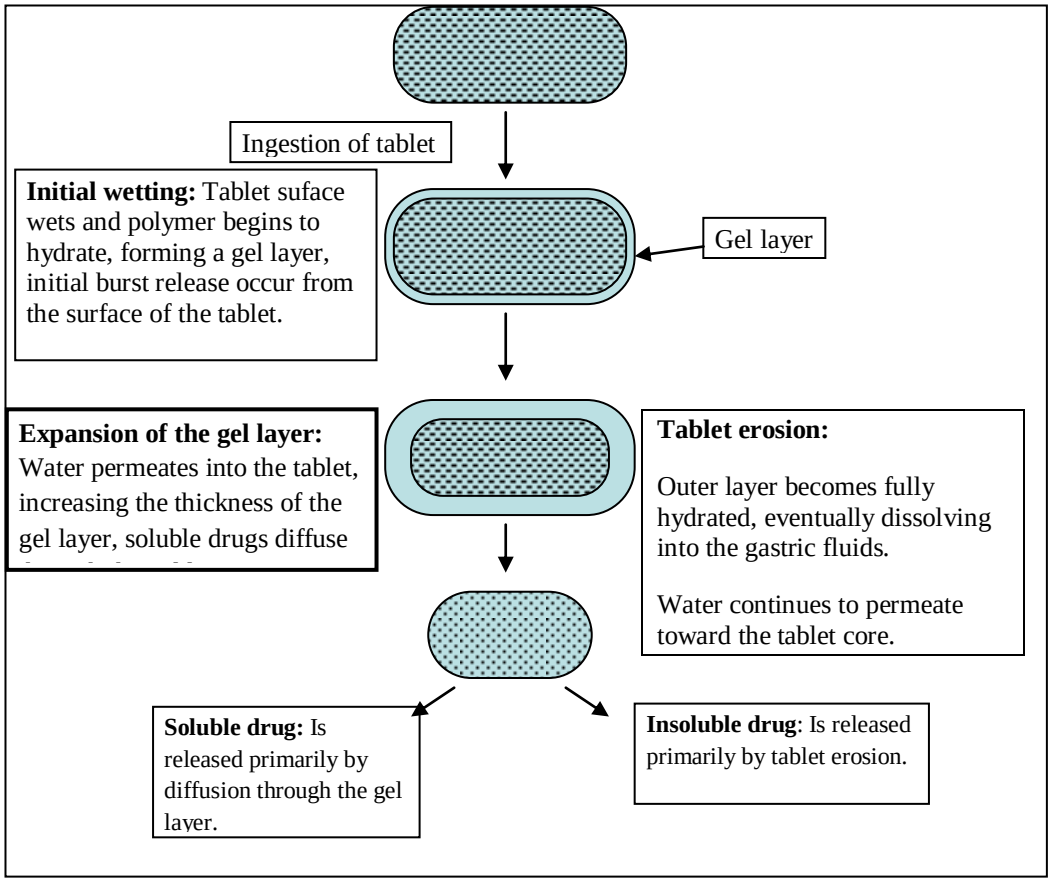


Fig. 6: Drug Release from Hydrophilic Matrix Tablet [20]

Advantages of Hydrophilic matrix tablets

With proper control of manufacturing process, reproducible release profiles are possible. They variability associated with them is slightly less than that characterizing coated release forms. Their capacity to incorporate active principles is large, which suits them to delivery of large doses[23].

Disadvantages of hydrophilic matrix tablet

For a hydrophilic sustained release matrix tablet, in which the release is mainly controlled by erosion of the swollen polymer gel barrier at the tablet surface, the presence of food may block the pores of the matrix and inhibit the drug release rate[19, 23].

4) Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to olegomers and monomers that can be metabolised or excreted.

Examples: natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5) Mineral Matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

1.1.2.2.2 On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity and consequently, macroporous; microporous and non-porous systems can be identified:

1) Macroporous Systems:

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2) Microporous System:

Diffusion in this type of system occurs essentially through pores. For microporous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

3) Non-porous System:

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

1.1.2.3 Polymers used in Matrix Tablets[24]:

- **Hydrogels**
  - -Polyhydroxyethyle methylacrylate (PHEMA)
  - -Cross-linked polyvinyl alcohol (PVA)
  - -Cross-linked polyvinyl pyrrolidone (PVP)
  - -Polyethylene oxide (PEO)
  - -Polyacrylamide (PA)
- **Soluble polymers**
  - -Polyethylene glycol (PEG)
  - -Polyvinyl alcohol (PVA)
  - -Polyvinyl pyrrolidone (PVP)
  - -Hydroxypropyl methyl cellulose (HPMC)

- **Biodegradable polymers**
  - -Polylactic acid (PLA)
  - -Polyglycolic acid (PGA)
  - -Polycaprolactone (PCL)
  - -Polyanhydrides
  - -Polyorthoesters
- **Nonbiodegradable polymers**
  - -Polyethylene vinyl acetate (PVA)
  - -Polydimethyl siloxane (PDS)
  - -Polyether urethane (PEU)
  - -Polyvinyl chloride (PVC)
  - -Cellulose acetate (CA)
  - -Ethyl cellulose (EC)
- **Mucoadhesive polymers**
  - -Polycarbophil
  - -Sodium carboxymethyl cellulose
  - -Polyacrylic acid
  - -Tragacanth
  - -Methyl cellulose
  - -Pectin
- **Natural gums**
  - -Xanthan gum
  - -Guar gum
  - -Karaya gum

1.1.2.4 Drug Release from Matrix systems[25, 26, 27, 28]:

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following **assumptions:**

a) A pseudo-steady state is maintained during drug release;

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;

d) The bathing solution provides sink conditions at all times.

- The release behaviour for the system can be mathematically described by the following equation:

$$\mathbf{dM/dh = C_o \,.\, dh - C_s/2} \qquad \text{Equation 1}$$

Where:

dM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix.

- Additionally, according to diffusion theory:

$$\mathbf{dM = (Dm.\, C_s \,/\, h).\, dt} \qquad \text{Equation 2}$$

Where:

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

dt = Change in time.

- By combining equation 1 and equation 2 and integrating:

$$\mathbf{M = [Cs.\, Dm.\, (2Co - Cs).\, t]^{1/2}} \qquad \text{Equation 3}$$

- When the amount of drug is in excess of the saturation concentration, then:

$$\mathbf{M = [2Cs \,.\, Dm \,.\, Co \,.\, t]^{1/2}} \qquad \text{Equation 4}$$

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line.

- Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

$$\mathbf{M = [Ds.Ca.p/T.\, (2C_o - p.Ca)\, t]^{1/2}} \qquad \text{Equation 5}$$

Where:

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusional pathlength.

- For pseudo steady state, the equation can be written as:

$$M = [2D.Ca .Co (p/T) t]^{1/2} \quad \text{Equation 6}$$

- The total porosity of the matrix can be calculated with the following equation:

$$p = pa + Ca/ \rho + Cex/ \rho ex \quad \text{Equation 7}$$

Where:

p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

Cex = Concentration of water soluble excipients.

- For the purpose of data treatment, equation 7 can be reduced to:

$$M = k. t^{1/2} \quad \text{Equation 8}$$

Where k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

• Initial concentration of drug in the matrix

• Porosity

• Tortuosity

• Polymer system forming the matrix

• Solubility of the drug.

Bimodal Release [29, 30, 31]:

In certain systems there is a bimodal or anomalous release of the active ingredient. In these systems there is diffusion; additionally, the extended release polymer may become hydrated and begin to dissolve leading to release upon erosion. These systems are complex and difficult to mathematically model since the diffusional path length undergoes change due to the polymer dissolution.

A series of transport phenomena are involved in the release of a drug from a swellable, diffusion/erodable matrix:

a) Initially, there are steep water concentration gradients at the polymer/water interface, resulting in absorption of water into the matrix.

b) Due to the absorption of water, the polymer swells, resulting in dramatic changes of drug and polymer concentration, increasing the dimensions of the system and increasing macromolecular mobility.

c) Upon contact with water the drug dissolves and diffuses out of the device.

d) With increasing water content, the diffusion coefficient of the drug increase substantially.

e) In the case of a poorly water-soluble drug, dissolved and undissolved drug coexist within the polymer-matrix.

f) Finally, the polymer itself dissolves.

These systems are described in terms of fronts. The following fronts have been defined, with regard to **Anomalous release systems:**

• The "**swelling front**", the erosion front, and the diffusion front. The swelling front separates the rubbery region (swelling polymer area) which has enough water absorbed within the polymer to lower the Tg of the polymer below the respective environmental temperature allowing for macromolecular mobility and swelling, from the non-swelling polymer region (where the polymer exhibits a Tg that is above the respective environmental temperature).

• The "**erosion front**" separates the matrix from the bulk solution and is the interface between the unstirred layer with polymer concentration gradient and the well stirred medium.

• The "**diffusion front**" is between the swelling and erosion front and separated the areas of non dissolved drug from the area of dissolved drug.

The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethylcellulose, hydroxypropylcellulose or tragacanth gums do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices.

- In 1985 Peppas introduced a semi-empirical equation describing the drug release behaviour from anomalous-release, hydrophilic matrix systems:

$$\mathbf{Q = k.\ t^{n}} \qquad \text{Equation 9}$$

Where:

Q = Fraction of drug release in time (t)

t = Time

k = Rate constant (incorporates characteristics of polymer system and drug)

n = Diffusional exponent

The value of n is indicative of the drug release mechanism.

- In order to describe relaxational transport, then modified equation 9 in order to account for relaxational transport:

$$Q = k_1 . t^n + k_2 . t^{2n} \quad \text{Equation 10}$$

Where:

k_1 = Fickian diffusion constant

k_2 = Relaxational mechanism constant

- If the surface area of the system is fixed, which is unlikely, the value of n should be 0.5 and equation 10 is transformed to:

$$Q = k_1 . t^{0.5} + k_2 . t \quad \text{Equation 11}$$

The first term of this equation accounts for diffusional phenomena, while the second term of this equation accounts for polymer erosion.

1.1.2.5 Effect of Release Limiting Parameter on Drug Release [32, 33, 34, 35]:

The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

A) Polymer hydration: It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linkings with the simultaneous forming of water-polymer linkings, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

B) Drug solubility: Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C) Solution solubility: In view of in vivo (biological) sink condition maintained actively by hemoperfusion; it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

D) Polymer diffusivity: The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion E_d has been acquired by

the diffusant is dependent on length of polymer chain segment, cross linking and crystallinity of polymer.

I) Polymer particle size: *Malamataris* stated that when the content of hydroxypropyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxypropyl methylcellulose led to the burst release.

II) Polymer viscosity: With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

III) Polymer concentration: An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

E) Thickness of polymer diffusional path: the controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

$$\mathbf{J_D = D\ dc/dx} \qquad \text{Equation 12}$$

J_D flux of diffusion across a plane surface of unit area where D is diffusibility of drug molecule, dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx.

F) Thickness of hydrodynamic diffusion layer: It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer $\delta_{d.}$

G) Drug loading dose: The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases.

In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain position with in the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non dissolved and thus not available for diffusion. The solid drug remains with in tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

H) Surface area and volume: The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the *in vitro* and *in vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form. *Siepman et al.* found that release from small tablet is faster than large cylindrical tablets.

I) Diluent's effect: The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

J) Additives: The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydrosoluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.[2]

1.1.3 Factor Influencing Oral Extended Release Dosage form Design:

1.1.3.1 Biological Factor[36, 37]

A. <u>Biological half-life</u>

Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency.

B. <u>Absorption</u>

The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorptions.

C. <u>Metabolism</u>

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite.

D. <u>Dosage form Index</u>

It is defined as the ratio of $C_{ss,max}$ to $C_{ss,min}$. Since the goal of controlled release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window, ideally its value should be as close to one as possible[37].

1.1.3.2 Physicochemical Factors[34,37]

A. Dose Size

In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

B. Ionization, pKa and Aqueous Solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

C. Partition Coefficient

Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells.

D. Stability

Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form[34, 36, 37].

1.1.4 Factors Influencing *In Vivo* Performance of Extended Release Dosage Formulations: [38]

There are various factors that can influence the performance of a sustained release product. The physiological, biochemical, and pharmacological factors listed below can complicate the evaluation of the suitability of a sustained release dosage formulation.

A. Physiological

- Prolonged drug absorption
- Variability in GI emptying and motility
- Gastrointestinal blood flow
- Influence of feeding on drug absorption

B. Pharmacokinetic/ Biochemical

- Dose dumping
- First- pass metabolism
- Variability in urinary pH; effect on drug elimination
- Enzyme induction/ inhibition upon multiple dosing

C. Pharmacological

- Changes in drug effect upon multiple dosing
- Sensitization/ tolerance

1.1.5 Drug Selection for Oral Extended Release Drug Delivery Systems:

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the Gastro Intestinal (G. I.) tract, the general absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient[11, 36, 37].

Table 1: Physicochemical Parameters for drug selection

Parameter	
Molecular weight/ size	< 1000 daltons
Solubility	> 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

The pharmacokinetic evaluation requires knowledge on a drug's elimination half- life, total clearance, absolute bioavailability, possible first- pass effect, and the desired steady concentrations for peak and trough[11, 36].

Table 2: Pharmacokinetic Parameters for Drug Selection

Parameter	
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V_d	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css av	The lower Css av and smaller V_d, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Disadvantages of Controlled Drug Delivery System[5, 6, 7, 8]

1. Decreased systemic availability in comparison to conventional dosage forms.
2. Poor in vitro - in vivo correlation.
3. Possibility of dose dumping due to food, physiologic or formulation variables, chewing or grinding of oral formulations by the patient.
4. Increased risk of toxicity.
5. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
6. Higher cost of formulation.

1.1.6 Evaluation of Extended Release Matrix tablet [39, 40]:

Invitro evaluation:

1.1.6.1 Hardness:

Hardness was measured using Monsanto hardness tester. For each batch three tablets were tested.

1.1.6.2 Friability: Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dusted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where, % F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

1.1.6.3 Weight Variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in Table-1 and none deviate by more than twice the percentage shown.

Table – 3: Percentage deviation allowed under weight variation test.

Average weight of tablet (mg)	Percentage deviation
130 or less	10
130-324	7.5
More than 324	5

1.1.6.4 Thickness:

Three tablets were selected randomly from each batch and thickness was measured by using vernical capliper.

1.1.6.5 In Vitro Release Study:

Standard USP or IP dissolution apparatus have been used to study in vitro release profile using both basket and rotating paddle. *In vitro* release rate study of matrix tablet of Drug X was carried out using the USP Apparatus 2 (Paddle apparatus) method. Medium used for release rate study was 500ml 6.8 Phosphate buffer during the course of study whole assembly was maintained at 50

rpm & at 37+0.5 ^{o}C temp. Withdraw a 10 ml of sample at specific time intervals like 1, 2, 4, 6, 8, 10, 12, 16, 18, 20 Hrs and replaced with 10 ml of fresh dissolution medium.

The withdrawn samples were dilute with dissolution medium if required and then filter it with whattman filter paper and assayed by UV Spectroscopy. The % release of drug was calculated .The observations for different batches are shown in succeeding tables. The percentage release of drug with respect to time for each batch, are graphically show.

1.2 INTRODUCTION TO DRUG X [41-48]

- **Description:** A White to almost white crystalline powder, practically odorless.
- **Molecular formula:** $(C_{15}H_{25}NO_3)_2.C_4H_6O_4$.
- **Molecular weight:** 652.81g/mol.
- **Category:** Potent beta blocker used in antihypertansive is now largely used as an antianginal and antiarrthymic. (Adrenergic Agents, Adrenergic beta-Antagonists, Anti-Arrhythmia Agents, Antiarrhythmic Agents, Antihypertensive Agents, Sympatholytics)
- **BCS class:** Class I.
- **Pka:** 9.6
- **Solubility:** Freely soluble in water, soluble in methanol, sparingly soluble in alcohol.

Media	**Solubility (mg/ml)**
Water	159.87
0.1 N HCL	157.95
4.5 pH acetate buffer	173.92
6.8 pH phosphate buffer	166.13
7.5 pH buffer	172.05

- **Half-life:** Plasma half-life ranges from approximately 3 to 7 hours.
- **Melting Point:** 135 - 140°C.
- **Mechanism of action:** The mechnanism of Drug X is as follows:
  - ✓ Competitive antagonism of catecholamines at peripheral adrenergic neuron sites, leading to decreased cardiac output.
  - ✓ A central effect leading to reduced sympathetic outflow to the periphery.
  - ✓ Suppression of rennin activity.
- **Pharmacokinetic Parameters:**
  - ➢ **Absorption:** After oral administration, the absorbance of the drug is variable and undergoes significant first pass metabolism. The onset of action is 1.5-4 hr after oral administration. In man, absorption of Drug X is rapid and complete. Plasma levels

following oral administration of conventional Drug X tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

- **Distribution:** Drug X crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin.
- **Metabolism:** Drug X is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Concomitant use of inhibiting drugs in poor metabolizers will increase blood levels of Drug X several-fold, decreasing Drug X'S cardioselectivity.
- **Elimination:** Elimination is mainly by biotransformation in the liver, less than 5% of an oral dose of Drug X is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity. Following intravenous administration of Drug X, the urinary recovery of unchanged drug is approximately 10%.

- **Protein binding:** Plasma proteins binding the compound is about 12 %.
- **Indications:** Indications for its use include:
  - Mild to moderate hypertension;
  - Congestive heart failure;
  - Following myocardial infarction in patients with clinical evidence of heart failure;
  - Susceptible patients over 55 years: prevention of myocardial infarction, stroke, cardiovascular death or need of revascularization procedures.
- **Overdosage**
  - **Symptoms**

Overdosage of Drug X may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness / coma, nausea, vomiting and cyanosis. Concomitant ingestion of alcohol, antihypertensives,

quinidine or barbiturates may aggravate the patient's condition. The first manifestations of overdosage may be observed 20 minutes to 2 hours after ingestion.

- **Management**

Induction of vomiting or gastric lavage. In the presence of severe hypotension, bradycardia and impending heart failure, administer a $beta_1$-agonist (e.g. prenalterol) intravenously at 2-5 minute intervals or as a continuous infusion until the desired effect is achieved. Where a selective $beta_1$-agonist is not available, dopamine may be used; or atropine sulphate IV may be used in order to block the vagus nerve. If a satisfactory effect is not achieved other sympathomimetic agents such as dobutamine or noradrenaline may be given. Glucagon in a dose of 1-10 mg can also be administered. A pacemaker may be necessary. A $beta_2$-agonist can be given IV to combat bronchospasm. The dosages of agents (antidotes) needed to treat overdose of beta-blockade are much higher than normally recommended therapeutic dosages. This is because beta-receptors are occupied by the beta-blocker.

- **Caution**

* Do not take during pregnancy as it may be harmful to the unborn baby. Seek further medical advice from your doctor. If you get pregnant while taking this medicine, stop taking it and consult your doctor immediately.
* Do not take during Breastfeeding because of this medicine passes into breast milk. The manufacturer states that it should not be taken by women who are breastfeeding. Women who need treatment with this medicine should not breastfeed.

1.3 INTRODUCTION TO POLYMERS

1.3.1 HydroxyPropyl MethylCellulose (HPMC) [49-51]

1. Nonproprietary Names

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum

USPNF: Hypromellose

2. Synonyms

Benecel MHPC; E464; Hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glucol ether; methyl Hydroxypropylcellulose; Metolose; Tylopur.

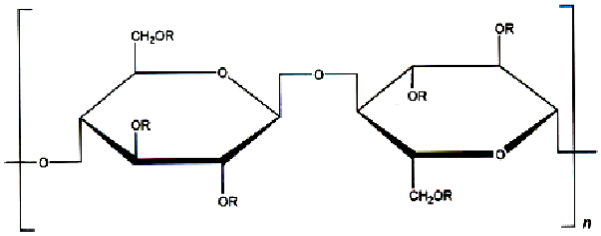
3. Chemical Name

Cellulose hydroxypropyl methyl ether

4. Molecular Weight

10,000- 150, 00, 00.

5. Structural Formula



6. Functional Category

Coating agent; Film former; rate controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7. Description

Hypromellose is an odor less and tasteless, White to creamy white powder.

8. Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulation. In oral products, hypromellose is primarily used as a tablet binder, in film coating and as a matrix for used in extended release tablet formulation. Depending upon the viscosity grad, is used for film coating solutions to film coat tablets. Hypromellose is also used as a suspending agents and thickening agent in topical formulation.

9. Pharmacopoeial Specifications

Hypromellose is official in JP, PhEur, and USP.

10. Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Use

Use	Concentration
Extended release-matrix former	15-35%
Tablet binder	2-6%
Tablet film coating	5%

Table 1: Typical viscosity values for 2% (w/v) aqueous solutions of Methocel

Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.). Viscosities measured at 20°C.

Methocel product	USP 28 designation	Nominal viscosity (mPa s)
Methocel K100 Premium	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel E10M Premium	2906	10 000
Methocel E3 Premium LV	2906	3
Methocel E5 Premium LV	2906	5
Methocel E6 Premium LV	2906	6
Methocel E15 Premium LV	2906	15
Methocel E50 Premium LV	2906	50
Metolose 60SH	2910	50, 4000, 10 000

11. Related Substances
Hydroxyethyl cellulose; hydroxyethylmethyl cellulose; hydroxypropyl cellulose; hypromellose phthalate; methylcellulose.

1.3.2 Hydroxypropyl Cellulose[49-51]

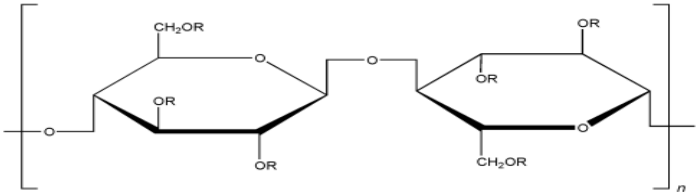
1. Nonproprietary Names
• BP: Hydroxypropylcellulose
• JP: Hydroxypropylcellulose
• PhEur: Hydroxypropylcellulosum
• USPNF: Hydroxypropyl cellulose

2. Synonyms
Cellulose, hydroxypropyl ether; E463; hyprolose; *Klucel*; *Methocel*; *Nisso HPC*; oxypropylated cellulose.

3. Chemical Name and CAS Registry Number
Cellulose, 2-hydroxypropyl ether [9004-64-2]

4. Molecular Weight
50 000–1 250 000.

5. Structural Formula



R is H or $[CH_2CH(CH_3)O]mH$

6. Functional Category
Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology
Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations; *see* Table I.

Table 2: Uses of hydroxypropyl cellulose.

Use	Concentration (%)
Extended release-matrix former	15-35

Tablet binder	2-6
Tablet film coating	5

Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations. Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

8. Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder.

9. Typical Properties

Acidity/alkalinity: pH = 5.0–8.5 for a 1% w/v aqueous solution.

Density (bulk): ≈0.5 g/cm3.

Interfacial tension: 12.5 mN/m for a 0.1% w/v aqueous solution compared with mineral oil.

Melting point: Softens at 130°C; chars at 260–275°C.

Particle size distribution:

• *Klucel* (regular grind), 95% through a US #30 mesh (590 μm), and 99% through a US #20 mesh (840 μm);
• *Klucel* (X-grind), 100% through a US #60 mesh (250 μm), and 80% through a US #100 mesh (149 μm).

Refractive index: *n*20D = 1.3353 for a 2% w/v aqueous solution.

Solubility: Hydroxypropyl cellulose is freely soluble in water below 38°C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45°C. Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as dimethyl formamide; dimethyl sulfoxide; dioxane; ethanol (95%); methanol; propan-2-ol (95%); and propylene glycol.

Specific gravity: 1.2224 for particles; 1.0064 for a 2% w/v aqueous solution at 20°C.

Viscosity (dynamic): A wide range of viscosity types are commercially available; Solutions should be prepared by gradually adding the hydroxypropyl cellulose to a vigorously stirred solvent. Increasing concentration produces solutions of increased viscosity.

Table 3: Viscosity of aqueous solutions of Klucel (Aqualon) at 25°C.

Grade	**Viscosity (mPa s) of various aqueous solutions of stated concentration**

	1%	2%	5%	10%
Klucel HF	1500-3000	-	-	-
Klucel MF	-	4000-6500	-	-
Klucel GF	-	150-400	-	-
Klucel JF	-	-	150-400	-
Klucel LF	-	-	75-150	-
Klucel EF	-	-	-	200-600

10. Stability and Storage Conditions
Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying. Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, resulting in chain scission and hence a decrease in solution viscosity. Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool, dry place.

11. Incompatibilities
Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions. The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration; Hydroxypropyl cellulose may not tolerate high concentrations of other dissolved materials.

12. Related Substances
Hydroxyethyl cellulose; hydroxypropyl cellulose, low-substituted; hypromellose.

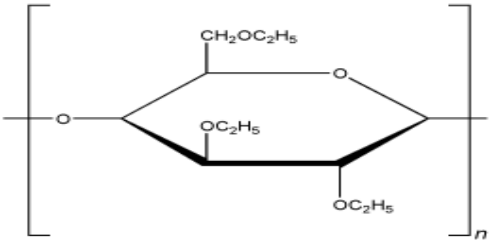
1.3.3 Ethyl cellulose[49-51]

1. Nonproprietary Names
• BP: Ethylcellulose
• PhEur: Ethylcellulosum
• USPNF: Ethylcellulose

2. Synonyms
Aquacoat ECD; *Aqualon*; E462; *Ethocel*; *Surelease*.

3. Chemical Name and CAS Registry Number
Cellulose ethyl ether [9004-57-3]

4. Structural Formula



5. Functional Category
Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

6. Description
Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder.

7.Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations.

Use	**Concentration (%)**
Microencapsulation	10-20
Sustained-release tablet coating	3-20
Tablet coating	1-3
Tablet granulation	1-3

8. Typical Properties

Density (bulk):
0.4 g/cm3

Glass transition temperature:
129–133°C26

Solubility:
ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Specific gravity:
1.12–1.15 g/cm3

Viscosity:

Table 4: Viscosity of Ethyl cellulose

Grade	Viscosity (mPa s)	Mean particle size (μm)
Ethocel Std 4 Premium	3-5.5	-
N-7	5.6-8	-
Ethocel Std 7FP Premium	6-8	5-15
Ethocel Std 7 Premium	6-8	310
T-10	8-11	-
N-10	8-11	-
Ethocel Std 10FP Premium	9-11	3-15
Ethocel Std 10P Premium	9-11	375
N-14	12-16	-
Ethocel Std 20P Premium	18-22	-
N-22	18-24	-
Ethocel Std 45P Premium	41-49	-
N-50	40-52	-
N-100	80-105	-
Ethocel Std 100FP Premium	90-110	30-60
Ethocel Std 100P Premium	90-110	465

9. Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

10. Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

11. Related Substances

Hydroxyethyl cellulose; hydroxyethylmethyl cellulose; methylcellulose.

2. AIM OF PRESENT INVESTIGATION

Modified oral drug delivery systems are based on single or multiple-unit reservoir or matrix system. Extended release products aim at releasing the drug continuously at a predetermined rate in order to increase the patient compliance and bioavailability. This is expected since the frequency of administration is reduced and peaks are cut to prevent high concentrations, locally or systemically, which can cause undesirable side effects. Thus, the tissue concentrations are kept at a low but effective level over an extended time period.

Drug X is a beta1-selective (cardioselective) adrenergic antagonist class sympatholytic drug. It is used in hypertension, cardiac failure and angina pectoris. When dose is missing it may causes nocturnal attack[52]. Drug X is well absorbed orally, but absolute oral bioavaibility average about 50% because of hepatic first pass metabolism. Its biological half life is (3-6 hours). Hence, in this work; an attempt is made to formulate extended release tablets of Drug X to increase bioavailability, patient compliance by reducing dosing frequency and to achieve even plasma concentration profile over 20 hrs.

Drug X is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the Drug X[53]. The most commonly used method of modulating the drug release is to include it in a matrix system[54,55]. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness and broad regulatory acceptance[56]. Hence the aim of present investigation was to develop Extended Release Matrix formulation of Drug X using HPMC, HPC and Ethyl cellulose and was evaluated by invitro study like Cumulative % release, hardness, thickness, friability etc…

3.1 LITERATURE REVIEW ON EXTENDED RELEASE TABLET

Hosseinali Tabandeh et al. [57] has studied sustained-release tablet formulation should ideally have a proper release profile insensitive to moderate changes in tablet hardness that is usually encountered in manufacturing. In this study, matrix Aspirin (acetylsalicylic acid) tablets with ethylcellulose (EC), Eudragit RS100 (RS), and Eudragit S100 (S) were prepared by direct compression. The release behaviors were then studied in two counterpart series of tablets with hardness difference of three Kp units, and compared by non-linear regression analysis. In the S-containing formulation, the release profile was completely sensitive to the hardness change. In RS-containing series, the slope of the release graph did not change due to the hardness decrease, but the y-intercept or the lag time in release was decreased. In EC-containing matrix tablets, both the slopes and the y-intercepts did not change by the decrease in hardness. In conclusion, EC with an amount as little as 10 percent in formulation could make sustained-release aspirin tablets in which the release profile is not sensitive to moderate changes in hardness.

R.K.KAR et al. [58] has investigated the design and characterization of oral controlled release matrix tablets of Zidovudine (AZT) in order to improve efficacy and better patient compliance. Tablets were prepared by direct compression method using various proportion of hydrophilic polymer viz; Eudragit RS100 and RL100 along or in combination with hydrophobic polymer ethyl cellulose. In vitro release studies were performed using USP type I apparatus (rotary basket type). The release kinetics was analysed using Zero-order model equation, Higuchi's square root equation and Korsmeyer and Peppas' emphirical equation. Dissolution study revealed that either Eudragit RS100 or RL100 10%,20% w/w of tablet preparations were able to sustain the drug release up to 9 hours, but 30%, 40% as well as ethyl cellulose combination with 20% and 25% w/w of Eudragit RS100 and RL100 were able to sustaining the drug release for 12 hour. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets followed non-Fickian diffusion mechanism. The optimized formulation (F13) showed insignificant difference in release mechanism as well as release kinetics ($P>0.05$) when stability study was done for six months at $40\pm2\ ^{0}C$ and 75±5% RH.

Anroop B. Nair et al. [59] has studied the utility of diverse grades of HPMC in developing a controlled release formulation for a hydrophilic drug, Enalapril maleate. Controlled release uncoated tablets were prepared by direct compression technique. Two grades of HPMC (K100 and K4M) in different proportions were used to prepare the tablets, and were evaluated for physical properties, drug content, in vitro drug release and drug release kinetics as well. All the formulations demonstrated good physical integrity and the drug content were in the official limits. The formulation with HPMC K100 (25 mg/tablet) and K4M (15 mg/tablet) have been found to release the required amount of drug (2.97 mg/h) through out the study period (14 h). The calculated regression coefficients showed higher r2 value with Higuchi model and zero order kinetics. Given the excellent release profile, the study concluded that HPMC in different grades with low concentration alone can control the enalapril maleate release over a period of time (14 h).

Seema Pushkar et al. [60] has developed the extended release tableted matrix devices for once daily dosing of Diclofenac sodium, and their evaluation for performance and compliance with official pharmacopoeial and allied pharmaceutical requirements. The matrix tablets were prepared by drug incorporated polymer matrix, formulated using different combinations and ratios of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (Sodium CMC), and sodium alginate (NaAlg). The drug loaded polymeric matrices so prepared were compressed to tablets and studied for drug the release behaviour and comparative kinetic characterization along with six popular marketed brands of Diclofenac – SR tablets. Dissolution testing for modeling of drug release kinetics was conducted as per the SUPAC guidelines provided by FDA for modified release dosage forms. The *in vitro* results shown a better release profile of formulated delivery system when compared to marketed brands extended up to 24 hours. The various formulations have shown an extended release up to 11 – 23 hours in different release environments.

M. HARRIS SHOAIB et al. [61] has developed a once-daily sustained release matrix tablet of Ibuprofen using hydroxypropyl methylcellulose (HPMC) as release controlling factor and to evaluate drug release parameters as per various release kinetic models. In order to achieve required sustained release profile tablets were directly compressed using Avicel pH 101 and Magnesium stearate. The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model were based on linearity (coefficient of correlation). The drug release data fit well to the Higuchi expression. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion.

RAGHAVENDRA RAO N. G et al. [62] has presented work on sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. After evaluation of physical properties of tablet, the *in vitro* release study was performed in 0.1 N HCl (pH 1.2) for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken. It was observed that matrix tablets contained polymer blend of HPMC/CG were successfully sustained the release of drug upto 12 hrs.

Mahesh Thube et al. [63] has formulated Pentoxifylline extended release matrix tablet of hydrophilic polymer HPMC K15M and hydrophobic polymer MCC 101 combination using 32 factorial designs. Pentoxifylline is the hemorrheologic agent, lowering blood viscosity, and improving erythrocyte flexibility. It is having half life 0.4 - 0.8 hours (1-1.6 hours for active metabolite) with the usual oral dose is 400 mg three times daily. Nine formulations were

prepared and dissolution studies were performed. The dissolution data obtained were fitted to the PCP disso version 3 software. Linear regression analysis and model fitting depicted that the formulations followed Peppas-Korsmeyer release mechanism. The two formulation variables were found to be significant for the release properties ($P < 0.05$). The quadratic mathematical model developed could be used to further predict formulations with desirable release. The similarity factor f2 was found to be 55.75 for the developed formulation indicating the release was similar to that of the marketed formulation (Trental). Thus, a combination of HPMC K15M and MCC 101 extends the release for a period of 24 hrs.

P.R. Radhika et al. [64] has developed a new monolithic matrix tablet to completely deliver Glipizide in a zero order manner over a sustained period. Two approaches were examined using drug in a formulation that contain polymer like hydroxylpropyl methylcellulose K 100 (HPMCK) and Eudragit L 100. The granules were prepared by wet granulation method. Technological characterizations (thickness, diameter, weight variation test, drug content, hardness, and friability) were conceded with the formulated matrix tablet and *in vitro* drug release was measured by means of dissolution apparatus. The kinetic release treatment showed that the release of drug follows zero order kinetic (r2= 0. 9959), Koresmeyer equation gave value of r2= 0.9853 which was close to one indicating that the drug was released by zero order kinetic. The identical plot for (log cumulative percentage drug release vs time) for Koresmeyer-Peppas equation indicated a good linearity for the commercially available sustained release tablet. Scanning electron microscope confirmed both diffusion and erosion mechanism for the optimized batch of matrix tablet.

Prisant LM et al. [65] applied biotechnical use of chemical-dispensing systems to propranolol, clonidine (the transdermal therapeutic system), nifedipine (the gastrointestinal therapeutic system), verapamil (the sodium alginate and spheroidal oral-delivery absorption system), felodipine (the hydrophilic gel principle) and diltiazem (one system comprising sustained-release beads and the other utilizing the patented Geomatrix extended-release system). Oral drug-delivery systems allow antihypertensive agents that previously had to be administered two to four times daily to be administered once each day. Potential disadvantages of the oral controlled-release products include delayed attainment of pharmacodynamic effect, unpredictable or reduced bioavailability, enhanced first-pass hepatic metabolism, dose dumping, sustained toxicity, dosing inflexibility, and increased cost. Potential advantages include reduced dosing frequency, enhanced compliance and convenience, reduced toxicity, stable drug levels, uniform drug effect, and decreased total dose.

3.2 LITERATURE REVIEW ON POLYMERS

Barakat NS et al. [66] investigated the effect of lipophilic (Compritol 888 ATO) and hydrophilic components (combination of HPMC and Avicel) on the release of carbamazepine from granules and corresponding tablet. Wet granulation followed by compression was employed for preparation of granules and tablets. The matrix swelling behavior was investigated. The dissolution profiles of each formulation were compared to those of Tegretol CR tablets and the mean dissolution time (MDT), dissolution efficiency (DE%), and similarity factor (f(2) factor) were calculated. It was found that increase in the concentration of HPMC results in reduction in the release rate from granules and achievement of zero-order is difficult from the granules. Increasing in drug loading resulted in acceleration of the drug release and in anomalous controlled-release mechanism due to delayed hydration of the tablets. These results suggest that wet granulation followed by compression could be a suitable method to formulate sustained release CBZ tablets.

Mandal U et al. [67] formulated new fixed dose combination of metformin hydrocholride (HCl) as sustained release and glipizide as immediate release as a bilayer matrix tablet using hydroxy propyl methyl cellulose (HPMC) as the matrix-forming polymer, and the tablets were evaluated via in vitro studies. Three different grades of HPMC (HPMC K 4M, HPMC K 15M, and HPMC K 100M) were used. All tablet formulations yielded quality matrix preparations with satisfactory tableting properties. In vitro release studies were carried out at a phosphate buffer of pH 6.8 with 0.75% sodium lauryl sulphate w/v using the apparatus I (basket) as described in the United States Pharmacopeia (2000). There was no significant difference in drug release for different viscosity grade of HPMC with the same concentration. Tablet thus formulated provided sustained release of metformin HCl over a period of 8 hours and glipizide as immediate release.

Huang YT et al. [68] formulated the sustained release matrix tablet of pyridostigmine bromide by direct compression of wet-extruded and spheronized core pellets with HPMC excipients and exhibited a zero-order sustained release (SR) profile. The 2(3) full factorial design was utilized to search an optimal SR tablet formulation. The results of moisture absorption by Karl Fischer meter showed the optimum SR tablet could improve the hygroscopic defect of the pure drug (PB). In the in vivo study, the results of the bioavailability data showed the T(max) was prolonged (from 0.65 +/- 0.082 hr to 4.83 +/- 1.60 hr) and AUC(0-t) (from 734.88 +/- 230.68 ng/ml.hr to 1153.34 +/- 488.08 ng/ml.hr) and was increased respectively for optimum PB-SR tablets when compared with commercial immediate release (IR) tablets. Furthermore, the percentages of in vitro dissolution and in vivo absorption in the rabbits have good correlation.

Md. Mofizur Rahman et al. [69] has evaluated the effect of hydrophilic polymers on the release profile of drug from matrix system. Salbutamol sulphate, an anti-asthmatic agent, was used as a model drug to evaluate its release characteristics from different matrices. Matrix tablets of salbutamol sulphate were prepared by direct compression process using methocel K100M CR polymer. Release kinetics of salbutamol sulphate from these sustained release matrices in distilled water using USP paddle method with sinker for 8 hours were studied. Statistically significant differences were found among the drug release profile from different formulations. Higher polymer content (70%) in the matrix decreased the rate of the drug due to increased

tortuosity and decreased porosity. At lower polymeric level (30%), the rate of drug release was elevated. The release mechanism was explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The results generated in this study showed that the profile and kinetics of drug release were functions of polymer type, polymer level and physico-chemical properties of the drug.

Marina Levina et al. [70] studies the influence of excipients on drug release from hydroxypropyl methylcellulose matrices. The influence of commonly used excipients, spray-dried lactose (SDL), microcrystalline cellulose (MCC), and partially pregelatinized maize starch (Starch 1500®) on drug release from hydroxypropyl methylcellulose (HPMC, hypromellose) matrix system has been investigated. A model formulation contained 30%w/w drug, 20%w/w HPMC, 0.5%w/w fumed silica, 0.25%w/w magnesium stearate, and 49.25%w/w filler. Chlorpheniramine maleate and theophylline were used as freely (1 in 4) and slightly (1 in 120) water-soluble drugs, respectively. It was found that for both drugs, addition of 20 to 49.25%w/w Starch 1500 resulted in a significant reduction in drug release rates compared to when MCC or SDL was used. The study showed that using lactose or microcrystalline cellulose in the formulations resulted in faster drug release profiles. Partially pregelatinized maize starch contributed to retardation of both soluble and slightly soluble drugs. This effect may be imparted through synergistic interactions between Starch 1500 and HPMC and the filler actively forming an integral part within the HPMC gel structure.

Emami J. et al. [71] investigated the In Vitro-in Vivo Evaluation of Sustained Release Lithium Carbonate Matrix Tablets to study the Influence of Hydrophilic Matrix Materials Sustained-release matrix tablets were therefore developed using different types and ratios of polymers including carbomer (CP), Na carboxymethylcellulose (Na CMC) and hydroxypropylmethylcellulose (HPMC), to assess the release profiles and in vivo performance of the formulations. The tablets were prepared by either direct compression (DC) or wet granulation (WG). The matrix tablets containing 15% CP exhibited suitable release kinetics and uniform absorption characteristics comparable to that of Eskalith. In vivo, this formulation produced a smooth and extended absorption phase very much similar to that of Eskalith with the identical elimination half-life and extent of absorption. The matrix tablets containing 15% CP reduces the incidence of side effects often associated with high serum concentration of Lithium and blood level variations. Direct correlation between the dissolution profiles and the relative bioavailability of the formulations could be observed.

Vueba ML et al [72] studies the Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets. The present work reports the study of different ketoprofen:excipient formulations, in order to determine the effect of the polymer substitution and type of diluent on the drug-release mechanism. Substituted cellulose-methylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose were used as polymers, while lactose monohydrate and beta-cyclodextrin were tested as diluents. Polymers MC25 and HPC were found not to be appropriate for the preparation of modified release ketoprofen hydrophilic matrix tablets, while HPMC K15M and K100M showed to be advantageous. The analysis of the release profiles in the light of distinct kinetic models (zero-order, first-order, Higuchi and Korsmeyer-Peppas) led to the conclusion that the type of polymer did not influence the release mechanism of the drug. The mean dissolution time (MDT) was determined, the highest MDT value being obtained for HPMC

formulations. Moreover, the drug-release process was found to be slightly influenced by the type of diluent, either lactose or beta-cyclodextrin.

Klausner EA et al.[73] developed the Itopride Floating drug delivery system. Itopride hydrochloride is the drug of first choice in the therapy of upper dyspepsia Optimized formulation F10 containing 125 mg HPMC K100M, 40 mg HPMC K15M, and 40 mg carbopol 934P was considerd as the best product with respect to in vitro drug release for 24 hours release action, total floating time and improved bioavailability and site-specific action. Tablets of batch F10 possessed quick buoyancy lag time of 110 sec. and good total floating time of 24 hrs. The results showed that the drug release rate was decreased as the viscosity of the polymer was increased.

Muhammad KS et al.[74] studied the Naproxen release from sustained release matrix system and effect of cellulose derivatives. The present study was conducted to investigate the low viscosity grades of hydroxypropylmethyl cellulose (HPMC) and ethyl cellulose (EC) in sustaining the release of water insoluble drug, naproxen from the matrix tablets. Both HPMC and EC were incorporated in the matrix system separately or in combinations by wet granulation technique. In vitro dissolution studies indicated that EC significantly reduced the rate of drug release compared to HPMC in 12 hour testing time. But, no significant difference was observed in the release profiles of matrix tablets made by higher percentages of EC. The tablets prepared with various combinations of HPMC and EC also failed to produce the desired release profiles. However, comparatively linear and desirable sustained release was obtained from EC-based matrix tablets prepared by slightly modifying the granulation method. Moreover, two different compression forces used in tableting had no remarkable effect on the release profile of naproxen.

Raghuram RK et al.[75] formulated and evaluated the Once-Daily Sustained Release Matrix Tablets of Nicorandil, a novel potassium channel opener used in cardiovascular diseases. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit RS-100, and polyvinylpyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, and sodium alginate. All the tablet formulations showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. The results of dissolution studies indicated that formulation containing drug-to-HPMC, 1:4; ethanol as granulating agent could extend the drug release up to 24 hours. In the further formulation development process, drug-to-HPMC, 1:4; EC 4% wt/vol as granulating agent, the most successful formulation of the study, exhibited satisfactory drug release in the initial hours, and the total release pattern was very close to the theoretical release profile. The mechanism of drug release from this formulation was diffusion coupled with erosion.

Bravo et al.[76] formulated the uncoated HPMC matrix tablets and evaluated the relationship and influence of different content levels of microcrystalline cellulose (MCC), starch and lactose in order to achieve a zero-order release of diclofenac sodium. They reported that release of diclofenac sodium was influenced by the presence of MCC and by the different concentrations of starch and lactose. Drug release kinetics from these formulations corresponded best to the zero-order kinetics. Compared to conventional tablets, release of the model drug from these HPMC

matrix tablets was prolonged. As a result, an oral controlled release dosage form to avoid the gastrointestinal adverse effects was achieved.

Elkhesen S. et al.,[77] formulated a hydrogel-forming bioadhesive drug delivery system for oral administration of verapamil HCl (VP). This system is a non-distintegrating gastro-retentive tablet to allow continuous slow release of VP in the stomach medium where it is more soluble. Different formulate of VP tablets were prepared by compression using various proportions of hydroxypropyl cellulose (HPC) and carbopol 934p (CP). The effect of polymer concentration on the release profile, water uptake and in vitro bioadhesion was studied. Five formulae (F3-F7) exhibited slow release profiles. Formulations F6 (40% HPC and 30% CP) and F7 (40% HPC and 40% CP) had the slowest. They showed 63.6 and 52.2% drug release, respectively, after 12 hours. The kinetic analysis of the release data demonstrated that the bigbest linearity were achieved when data fitted in Higuchi equation rather than zero or first order equations. They had n values close to 0.5 that confirming their Higuchi diffusion. F3 showed the highest swelling index (101.2%), however, the detachment force was intermediate (1.427 N/cm2). Formulae (F4-F7) showed relatively strong in-vitro bioadhesive force. They had detachment forces higher than 1 N/cm2. In general, a delay in drug release and an increase in the in-vitro bioadhesion was seen with the increase in both polymer concentrations. The in vitro data revealed that Formulae F4-F7 served the dual purpose of bioadhesion and sustained release.

Shinichiro Tajir et al., [78] has developed an extended-release dosage form of cevimeline. Two types of extended-release tablets (simple matrix tablets and press-coated tablets) were prepared and their potential as extended-release dosage forms were assessed. Simple matrix tablets have a large amount of hydroxypropylcellulose as a rate-controlling polymer and the matrix is homogeneous throughout the tablet. The press-coated tablets consisted of a matrix core tablet, which was completely surrounded by an outer shell containing a large amount of hydroxypropylcellulose. The simple matrix tablets could not sustain the release of cevimeline effectively. In contrast, the press-coated tablets showed a slower dissolution rate compared with simple matrix tablets and the release curve was nearly linear. The dissolution of cevimeline from the press-coated tablets was not markedly affected by the pH of the dissolution medium or by a paddle rotating speed over the range of 50–200 rpm. Furthermore, cevimeline was constantly released from the press-coated tablets in the gastrointestinal tract and the steady-state plasma drug levels were maintained in beagle dogs. These results suggested that the designed PC tablets have a potential for extended-release dosage forms.

4.1 MATERIAL & EQUIPMENTS

4.1.1 Materials used in the present investigation:

Table 4.1: Materials used in the present investigation

Sr. No.	Materials	Manufacturer/Supplier
1.	Drug X	Cadila Healthcare ltd, Ankleshvar, India.
2.	Ethyl cellulose 45cps	Aqualon polymers, India.
3.	HPMC K 100M	Signet chemicals, India.
4.	HPC Klucel-HXF	Ashland, India.
5.	PVP K 90	
6.	HPMC E4M	Dow Chemicals, India.
7.	Hydrogenated castor oil (HCO)	Cognis, India.
8.	Eudragit NE 40 D	Evonik industries, India.
9.	Stearic acid	Merk, Mallinckrodt.
10.	Gaur gum	Vapi Care Pharma Pvt Ltd, India.
11.	Microcrystalline Cellulose pH102	FMC Biopolymer, India.
12.	Magnesium Stearate	Amishi drugs & Chemicals, Ahmedabad, India.
13.	Colloidal silicon dioxide (Aerosil 200)	Shin Estu, Evonic.

4.1.2 Equipments / Machine used in the present investigation

Table 4.1.2: Equipments / Machine used in the present investigation

Sr. No.	Equipments/ Machine	Manufacturer/Supplier
1.	Electronic weighing balance (PG 403-S)	Mettler Toledo, Denver Instrument, India.
2.	Cage Blender	Cadmach machinery Co., Pvt. Ltd., Ahmedabad, India.
3.	Bulk Density measurement apparatus (ETD-1020)	Electro lab, India.
4.	"D" Tooling 8 Station Tablet compression machine	Cadmach machinery Co., Pvt. Ltd., Ahmedabad, India
5.	Tablet Hardness Tester (VK 200)	Benchsavertm Series,(VANKEL). India.
6.	Friability test apparatus (EF-1W, EF-2)	Electro lab, India
7.	Vernier caliper	Omega Instruments Ltd., India.
8.	Dissolution Test Apparatus (TDT-06T)	Electrolab, Mumbai, India.
9.	UV Spectrophotometer	UV-1700 Double beam Spectrophotometer, Shimadzu (Kyoto, Japan.).
10.	Quadro Co-mill	Quadro engineering, Waterloo, Canada

4.2 ANALYTICAL METHOD DEVELOPMENT

4.2.1 Determination of λ_{max} of Drug X:

Preparation of standard of Drug X: 100 µg/ml Drug X in Distilled water, 0.1 N HCL & 6.8 pH Phosphate buffer.

↓

Scanned it in the range of 200 nm to 400 nm by UV spectrophotometer.

↓

λ_{max} of Drug X in Distilled water, 0.1 N HCL & 6.8 pH Phosphate buffer was found to be **274 nm.**

At λ_{max}= 274 nm, Absorbance = 0.437 in D.W.

Absorbance = 0.429 in 0.1 N HCL.

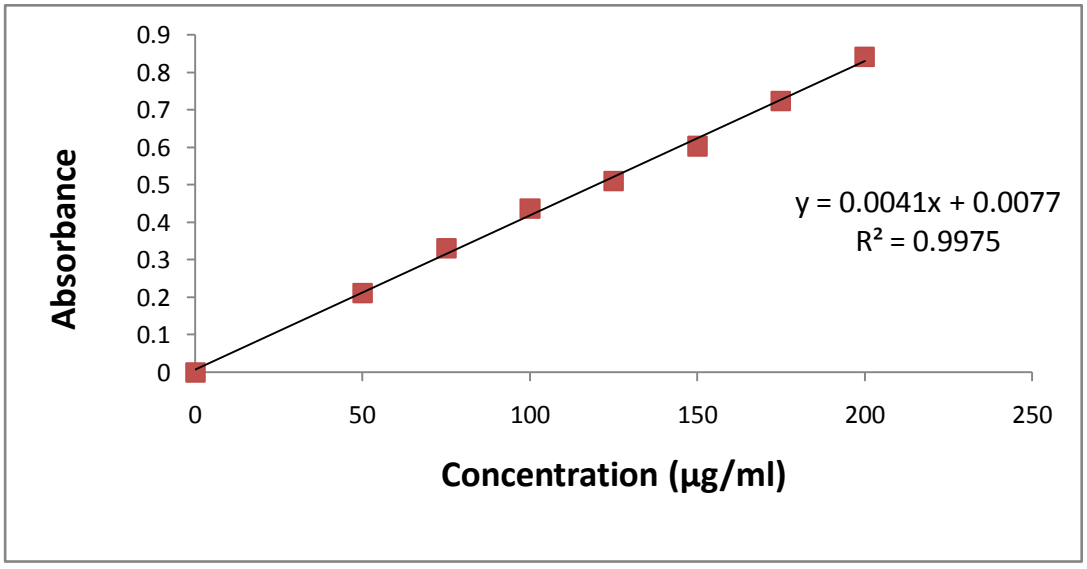
Absorbance = 0.415 in 6.8 pH Phosphate buffer.

4.2.2 PREPARATION OF STANDARD CURVE OF DRUG X IN D.W.

Standard (Stock) solution: 50 mg Drug X was dissolved in D.W. and volume was made up to 50 ml in 50 ml volumetric flask. This stock solution was 1000 µg/ml. This Stock solution was diluted with D.W. to make the concentration of 50, 75, 100…200 µg/ml. Absorbance of each solution was measured at λ_{max}: 274 nm using UV spectrophotometer by using D.W. as a reference standard.

Standard curve of Drug X in D.W. at λ_{max}: 274 nm

Concentration (µg/ml)	Absorbance 1	Absorbance 2	Absorbance 3	Average Absorbance	RSD (%)
0.00	0.00	0.00	0.00	0.00	0.00
50	0.210	0.212	0.214	0.212	0.943
75	0.329	0.331	0.334	0.331	0.759
100	0.435	0.437	0.438	0.436	0.349
125	0.508	0.510	0.513	0.510	0.493
150	0.602	0.603	0.605	0.603	0.253
175	0.722	0.724	0.726	0.724	0.276
200	0.840	0.841	0.843	0.841	0.181



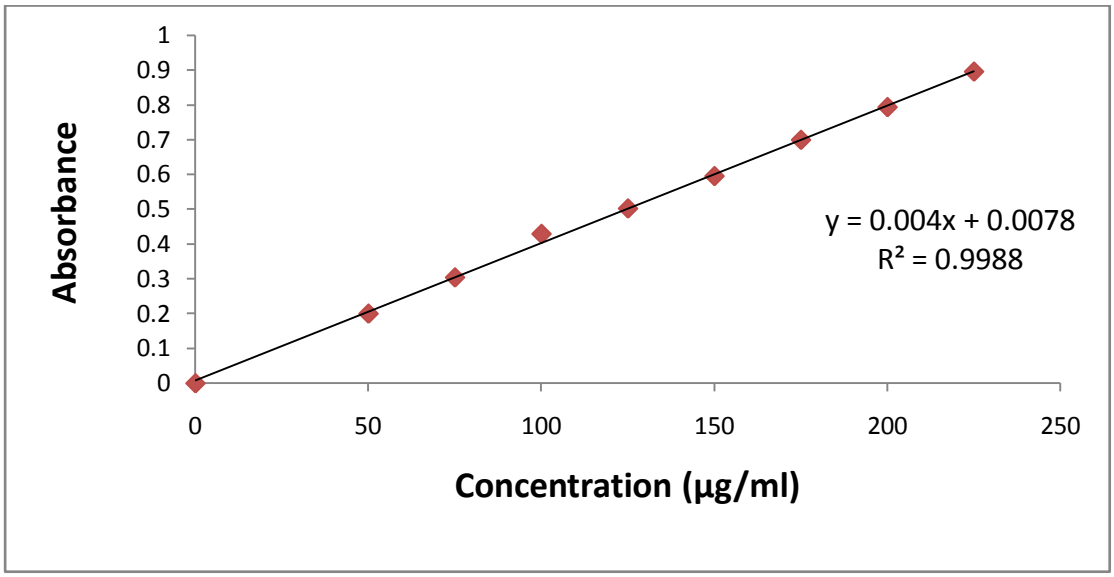
Slope	**0.0041**
Y-intercept	**0.0077**
R^2 value	**0.9975**

4.2.3 PREPARATION OF STANDARD CURVE OF DRUG X IN 0.1N HCl

Standard (Stock) solution: 50 mg Drug X was dissolved in 0.1N HCl and volume was made up to 50 ml in 50 ml volumetric flask. This stock solution was 1000 µg/ml. This Stock solution was diluted with 0.1N HCl to make the concentration of 50, 75, 100…225 µg/ml. Absorbance of each solution was measured at λ_{max}: 274 nm using UV spectrophotometer by using 0.1N HCl as a reference standard.

Standard curve of Drug X in 0.1N HCl at λ_{max}: 274 nm

Concentration (µg/ml)	Absorbance 1	Absorbance 2	Absorbance 3	Average Absorbance	RSD (%)
0	0.00	0.00	0.00	0.00	0.00
50	0.198	0.200	0.205	0.201	1.793
75	0.301	0.304	0.307	0.304	0.986
100	0.425	0.429	0.431	0.428	0.713
125	0.499	0.502	0.506	0.502	0.699
150	0.593	0.595	0.597	0.595	0.336
175	0.694	0.699	0.701	0.698	0.516
200	0.790	0.793	0.796	0.793	0.378
225	0.892	0.895	0.898	0.895	0.335



Slope	**0.004**
Y-intercept	**0.0078**
R^2 value	**0.9988**

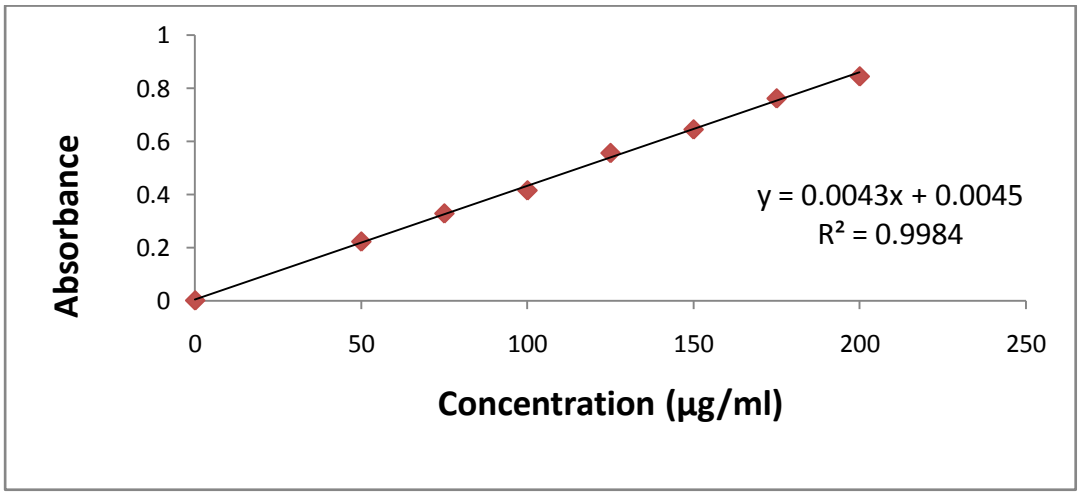
4.2.4 PREPARATION OF STANDARD CURVE OF DRUG X IN 6.8 pH PHOSPHATE BUFFER

Preparation 6.8 pH Phosphate Buffer [79]: 68 gm Potassium dihydrogen phosphate and 9.3gm NaOH pellet were dissolved in 10 liter Distilled water.

Standard (Stock) solution: 50 mg Drug X was dissolved in 6.8 pH Phosphate buffer and volume was made up to 50 ml in 50 ml volumetric flask. This stock solution was 1000 µg/ml. This Stock solution was diluted with 6.8 pH Phosphate buffer to make the concentration of 50, 75, 100…200 µg/ml. Absorbance of each solution was measured at λ_{max}: 274 nm using UV spectrophotometer by using 6.8 pH Phosphate buffer as a reference standard.

Standard curve of Drug X in 6.8 pH Phosphate buffer at λ_{max}: 274 nm

Concentration (µg/ml)	Absorbance 1	Absorbance 2	Absorbance 3	Average Absorbance	RSD (%)
0	0.00	0.00	0.00	0.00	0.00
50	0.220	0.222	0.225	0.222	1.131
75	0.325	0.328	0.330	0.327	0.768
100	0.411	0.415	0.418	0.414	0.846
125	0.552	0.556	0.559	0.555	0.632
150	0.643	0.645	0.648	0.645	0.389
175	0.760	0.762	0.765	0.762	0.330
200	0.842	0.845	0.848	0.845	0.355



Slope	0.0043

Y-intercept	**0.0045**
R^2 value	**0.9984**

4.3 FORMULATION DEVELOPMENT AND EVALUATION

FORMULA- F1:

- Total tablet weight = 250 mg
- Drug: HPMC K1OOM (1:1)

Sr no.	Ingredients	Quantity(mg) (For 1 Tablet)	Quantity(gm) (For 500 Tablets)	Percentage (%)
1	Drug X	47.5	23.75	19.0
2	**HPMC K100M**	**47.5 (1:1)**	**23.75**	**19.0**
3	PVP K90 (in water)	12.5	6.25	5.0
4	MCC 102	137.5	68.75	36.0
5	Aerosil 200	2.5	1.25	1.0
6	Megnesium stearate	2.5	1.25	1.0
	Total	250	125	100.0

Procedure (Wet granulation): Weigh accurate Drug X, HPMC K1OOM and MCC 102. Mixed them properly and granulated them by Wet granulation method using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability	Cumulative % release	
			1 hr	2 hr
90-100 N	4.78 mm	0.067%	50%	Nearest to 100%

Dissolution: Dissolution of tablet was performed as per method given in section: 1.1.6.5.

Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 2 hrs, so further combination of Polymers and optimization of Polymer concentration required to achieve desired drug release up to 20 hrs.

Conclusion: Tablets were further prepared by using combination of polymers and increasing the concentration of polymer to achieve desired drug release.

FORMULA- F2 & F3:

- Total tablet weight = 250 mg
- Drug: HPMC K1OOM (1:1)
- Drug: HPC Klucel- HXF (1:0.5), (1:1)

Sr no.	Ingredients	F2 Quantity(mg) (For 1 Tablet)	F3 Quantity(mg) (For 1 Tablet)
1	Drug X	47.5	47.5
2	HPMC K100M	47.5 (1:1)	47.5 (1:1)
3	**HPC Klucel- HXF**	**23.75 (1:0.5)**	**47.5 (1:1)**
4	PVP K90 (in water)	12.5	12.5
5	MCC 102	113.75	90
6	Aerosil 200	2.5	2.5
7	Megnesium stearate	2.5	2.5
	Total	250	250

Procedure (Wet granulation): Weigh accurate Drug X, HPMC K1OOM, HPC Klucel- HXF and MCC 102 as per formula. Mixed them properly and granulated them by Wet granulation method using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability	Cumulative % release		
			1 hr	2 hr	4 hr
90-100 N	4.81 mm	0.065%	25%	50%	Nearest to 100%

Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 4 hrs. So further optimization of Polymer concentration required to achieve desired drug release up to 20 hrs.

Conclusion: Tablets were further prepared by increasing the concentration of polymers to achieve desired drug release.

FORMULA- F4:

- Total tablet weight = 250 mg
- HPMC K1OOM (25%)
- Drug: HPC Klucel- HXF (25%)

Sr no.	Ingredients	Quantity(mg) (For 1 Tablet)	Quantity(gm) (For 500 Tablets)	Percentage (%)
1	Drug X	47.5	23.75	19.0
2	**HPMC K100M**	62.5	31.25	**25.0**
3	**HPC Klucel- HXF**	62.5	31.25	**25.0**
4	PVP K90 (in water)	12.5	6.25	5.0
5	MCC 102	60	30	24.0
6	Aerosil 200	2.5	1.25	1.0
7	Megnesium stearate	2.5	1.25	1.0
	Total	250	125	100.0

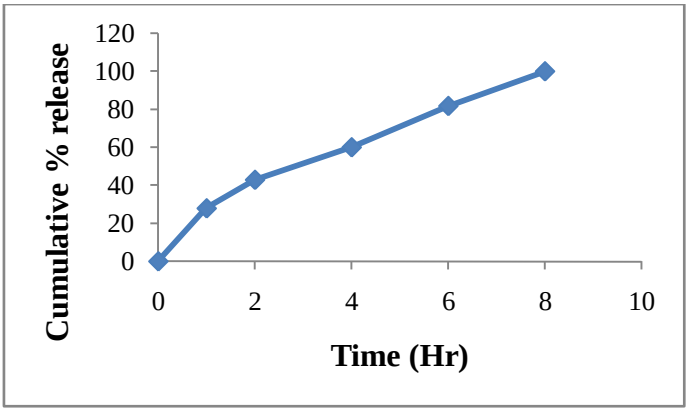
Procedure (Wet granulation): Weigh accurate Drug X, HPMC K1OOM, HPC Klucel- HXF and MCC 102. Mixed them properly and granulated them by Wet granulation method using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability	Cumulative % release
90-100 N	4.82 mm	0.065%	Nearest to 100% drug release up to 8 hrs.

Time (Hr)	Cumulative % release
0	0

1	27.89473684
2	42.89473684
4	60.01578947
6	81.76052632
8	99.98947368



Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 8 hrs, so further optimization and combination of Polymers required to achieve desired drug release up to 20 hrs.

Conclusion: Tablet was further prepared by using combination of other polymers, optimization of polymer concentration and by changing the method of preparation to achieve desired drug release.

FORMULA- F5 & F6:

- Total tablet weight = 250 mg
- Eudragit NE 40 D: 20 & 30 %

Sr no.	Ingredients	F5 Quantity(mg) (For 1 Tablet)	F6 Quantity(mg) (For 1 Tablet)
1	Drug X	47.5 (19%)	47.5 (19%)
2	**Eudragit NE 40 D**	**50 (20%)**	**75 (30%)**
3	MCC 102	147.5 (59%)	122.5 (49%)
4	Aerosil 200	2.5 (1%)	2.5 (1%)
5	Megnesium stearate	2.5 (1%)	2.5 (1%)
	Total	250	250

Procedure (Wet granulation): Weigh accurate Drug X and MCC 102. Mixed them properly and granulated them by Wet granulation method using Eudragit NE 40 D dispersion as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability
90-100 N	4.8 mm	0.06%

Result and Discussion: Eudragit NE 40 D could not provide sustained release of Drug X and good result could not get because of breaking of tablet in water within 1 hr. So further optimization and combination of other Polymers required to achieve desired drug release up to 20 hrs.

Conclusion: Tablet was further prepared by using combination of other polymers, optimization of polymer concentration and by changing the method of preparation to achieve desired drug release.

FORMULA- F7 & F8:

- Total tablet weight = 250 mg
- Gaur gum: 20 & 30%

Sr no.	Ingredients	F7 Quantity(mg) (For 1 Tablet)	F8 Quantity(mg) (For 1 Tablet)
1	Drug X	47.5 (19%)	47.5 (19%)
2	**Gaur gum**	**50 (20%)**	**75 (30%)**
3	PVP K90 (in water)	12.5 (5%)	12.5 (5%)
4	MCC 102	135 (54%)	110 (44%)
5	Aerosil 200	2.5 (1%)	2.5 (1%)
6	Megnesium stearate	2.5 (1%)	2.5 (1%)
	Total	250	250

Procedure (Wet granulation): Weigh accurate Drug X, Gaur gum and MCC 102. Mixed them properly and granulated them by Wet granulation method using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability
90-100 N	4.83 mm	0.065%

Result and Discussion: Tablet caused burst release of Drug X in water within 15 mins. Because of Gaur gum require some time to swell, 50% drug was released in lag time before the swelling of Gaur gum. Gaur gum could not provide sustained release of Drug X. So further optimization and combination of other Polymers required to achieve desired drug release up to 20 hrs.

Conclusion: Tablet was further prepared by using combination of other polymers, optimization of polymer concentration and by changing the method of preparation to achieve desired drug release.

FORMULA- F9 & F10:

- Total tablet weight = 250 mg
- Hydrogenated castor oil (HCO): 20 & 30 %

Sr no.	Ingredients	F9 Quantity(mg) (For 1 Tablet)	F10 Quantity(mg) (For 1 Tablet)
1	Drug X	47.5 (19%)	47.5 (19%)
2	Hydrogenated castor oil (HCO) (Powder form)	**50 (20%)**	**75 (30%)**
3	PVP K90 (in water)	12.5 (5%)	12.5 (5%)
4	MCC 102	135 (54%)	110 (44%)
5	Aerosil 200	2.5 (1%)	2.5 (1%)
6	Megnesium stearate	2.5 (1%)	2.5 (1%)
	Total	250	250

Procedure (Wet granulation): Weigh accurate Drug X, HCO and MCC 102. Mixed them properly and granulated them by Wet granulation method using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability

90-100 N	4.8 mm	0.072%

Result and Discussion: HCO could not provide sustained release of Drug X and good result could not get because of breaking of tablet at middle part in water within 2 hrs and due to capping and sticking problem during compression. So to avoid this problem, HPMC K100M was used in combination with HCO to achieve desired drug release up to 20 hrs.

Conclusion: Tablet was further prepared by using HPMC K100M in combination with HCO to achieve desired drug release.

FORMULA- F11:

- Total tablet weight = 250 mg
- Drug: HPMC K100M (1:1)
- Drug: Hydrogenated castor oil (HCO) (1:1)

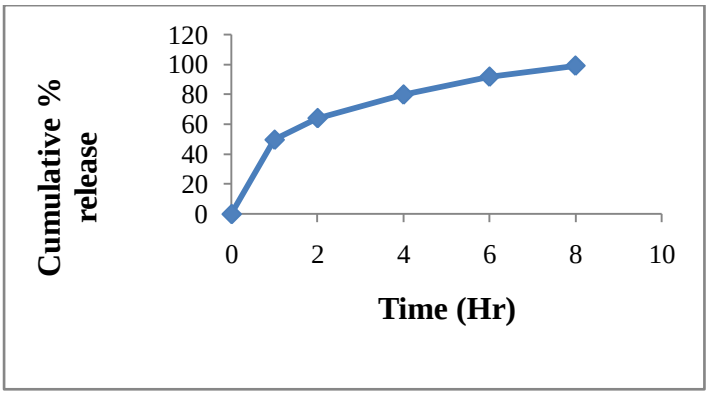
Sr no.	**Ingredients**	**Quantity(mg) (For 1 Tablet)**	**Quantity(gm) (For 500 Tablets)**	**Percentage (%)**
1	Drug X	47.5	23.75	19.0
2	HPMC K100M	**47.5 (1:1)**	23.75	19.0
3	Hydrogenated castor oil (HCO) (Powder form)	**47.5 (1:1)**	23.75	19.0
4	PVP K90 (in water)	12.5	6.25	5.0
5	MCC 102	90	45	44.0
6	Aerosil 200	2.5	1.25	1.0
7	Megnesium stearate	2.5	1.25	1.0
	Total	250	125	100.0

Procedure (Wet granulation): Weigh accurate Drug X, HPMC K100M, HCO and MCC 102. Mixed them properly and granulated them by Wet granulation method using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability	Cumulative % release
90-100 N	4.81 mm	0.06%	Nearest to 100% drug release up to 8 hrs.

Time (Hr)	Cumulative % release
0	0
1	49.73684211
2	64.21052632
4	79.97105263
6	91.92894737
8	99.30263158



Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 8 hrs, so further optimization and combination of Polymers required to achieve desired drug release up to 20 hrs.

Conclusion: Tablet was further prepared by using combination of other polymers, optimization of polymer concentration and by changing the method of preparation to achieve desired drug release.

FORMULA- F12:

- Total tablet weight = 200 mg
- Stearic acid: 20% to drug

Sr no.	Ingredients	Quantity(mg) (For 1 Tablet)	Quantity(gm) (For 500 Tablets)	Percentage (%)
1	Drug X	47.5	23.75	23.75
2	**Stearic acid**	9.5	4.75	**20% to drug**
3	IPA	q.s.	q.s.	
4	MCC 102	139	69.5	69.5
5	Aerosil 200	2	1	1.0
6	Megnesium stearate	2	1	1.0
	Total	200	100	100.0

Procedure (Melt granulation, Direct compression): First weigh stearic acid and melt it on hot plate at 60^0 to 70^0 C temperature. Add Drug X and IPA (q.s.) for resolidification. Solid granules were dried below 50^0C temperature and passed dried granules through 24 # sieve. Mix MCC 102, Mg stearate and Aerosil 200 with them. Then Tablet was prepared by Direct compression method using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability

90-100 N	3.55-3.59 mm	0.04%

Result and Discussion: Stearic acid could not provide sustained release of Drug X and good result could not get because of immediately breaking of tablet in water. So to avoid this problem, HPMC K100M was used in combination with stearic acid to achieve desired drug release up to 20 hrs.

Conclusion: Tablet was further prepared by using HPMC K100M in combination with stearic acid to achieve desired drug release.

FORMULA- F13:

- Total tablet weight = 200 mg
- Stearic acid: 20% to drug
- HPMC K100M: 28.75% to tablet wt.

Sr no.	Ingredients	Quantity(mg) (For 1 Tablet)	Quantity(gm) (For 500 Tablets)	Percentage (%)
1	Drug X	47.5	23.75	23.75
2	Stearic acid	9.5	4.75	**20% to drug**
3	IPA	q.s.	q.s.	
4	**HPMC K100M**	57.5	28.75	**28.75**
5	MCC 102	81.5	40.75	40.75
6	Aerosil 200	2	1	1.00
7	Megnesium stearate	2	1	1.00
	Total	200	100	100.0

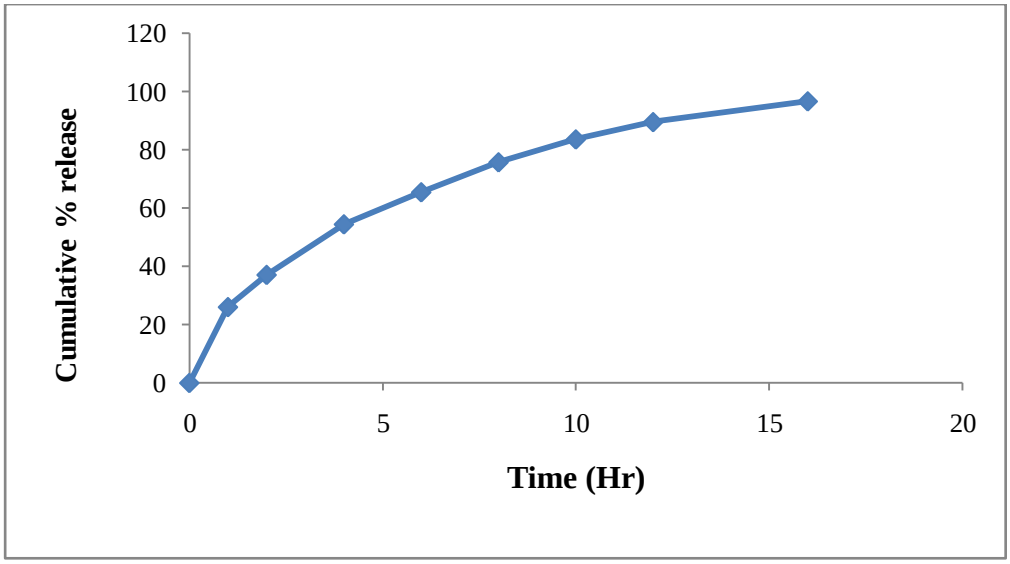
Procedure (Melt granulation, Direct compression): First weigh stearic acid and melt it on hot plate at 60^0 to 70^0 C temperature. Add Drug X and IPA (q.s.) for resolidification. Solid granules were dried below 50^0C temperature and passed dried granules through 24 # sieve. Mix HPMC K100M, MCC 102, Mg stearate and Aerosil 200 with them. Then Tablet was prepared by Direct compression method using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability	Cumulative % release
90-100 N	3.89-4.0 mm	0.04%	Nearest to 100% drug release up to 16 hrs.

Cumulative % release:

Time (hr)	Abs	Conc. in µg/ml	Conc. in µg/10 ml	Cumulative conc. (µg)	Cumulative conc. (mg)	Conc.(µg) in 500ml	Conc.(mg) in 500ml	Cumulative conc. (mg)	Cumulative % release
0	0	0	0	0	0	0	0	0	0
1	0.099	24.75	247.5	0	0	12375	12.375	12.375	26.0526
2	0.141	35.25	352.5	247.5	0.2475	17625	17.625	17.625	37.1052
4	0.205	51.25	512.5	600	0.6	25625	25.625	25.8725	54.4684
6	0.244	61	610	1112.5	1.1125	30500	30.5	31.1	65.4736
8	0.279	69.75	697.5	1722.5	1.7225	34875	34.875	35.9875	75.7631
10	0.304	76	760	2420	2.42	38000	38	39.7225	83.6263
12	0.321	80.25	802.5	3180	3.18	40125	40.125	42.545	89.5684
16	0.342	85.5	855	3982.5	3.9825	42750	42.75	45.93	96.6947



Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 16 hrs and greater than 25% drug release in 1 hr. So to control drug release in starting 1 hr, further HPMC E4M was used in combination with HPMC K100M to achieve desired drug release up to 20 hrs.

Conclusion: Tablet was further prepared by using HPMC E4M in combination with HPMC K100M to achieve desired drug release.

FORMULA- F14:

- Total tablet weight = 200 mg
- Stearic acid: 20% to drug
- HPMC K100M: 28.75%, HPMC E4M: 20% to tablet wt.

Sr no.	Ingredients	Quantity(mg) (For 1 Tablet)	Quantity(gm) (For 500 Tablets)	Percentage (%)
1	Drug X	47.5	23.75	23.75
2	Stearic acid	9.5	4.75	**20% to drug**
3	IPA	q.s.	q.s.	
4	HPMC K100M	57.5	28.75	28.75
5	**HPMC E4 M**	40	20	**20.00**
6	MCC 102	41.5	20.75	20.75
7	Aerosil 200	2	1	1.00
8	Megnesium stearate	2	1	1.00
	Total	200	100	100.0

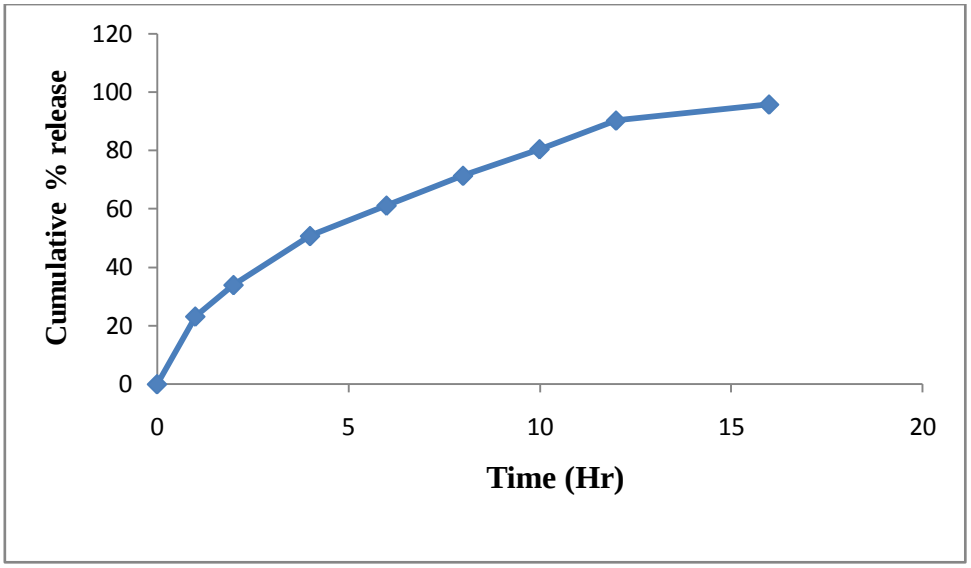
Procedure (Melt granulation, Direct compression): First weigh stearic acid and melt it on hot plate at 60^0 to 70^0 C temperature. Add Drug X and IPA (q.s.) for resolidification. Solid granules were dried below 50^0C temperature and passed dried granules through 24 # sieve. Mix HPMC K100M, HPMC E4M, MCC 102, Mg stearate and Aerosil 200 with them. Then Tablet was prepared by Direct compression method using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability	Cumulative % release
90-100 N	4.0 mm	0.06%	Nearest to 100% drug release up to 16 hrs.

Cumulative % release:

Time (hr)	Abs	Conc. in µg/ml	Conc. in µg/10 ml	Cumulative conc. (µg)	Cumulative conc. (mg)	Conc.(µg) in 500ml	Conc.(mg) in 500ml	Cumulative conc. (mg)	Cumulative % release
0	0	0	0	0	0	0	0	0	0
1	0.088	22	220	0	0	11000	11.00	11.00	23.1578
2	0.129	32.25	322.5	220	0.22	16125	16.125	16.125	33.9473
4	0.191	47.75	477.5	542.5	0.5425	23875	23.875	24.095	50.7263
6	0.228	57	570	1020	1.02	28500	28.5	29.0425	61.1421
8	0.263	65.75	657.5	1590	1.59	32875	32.875	33.895	71.3578
10	0.293	73.25	732.5	2247.5	2.2475	36625	36.625	38.215	80.4526
12	0.325	81.25	812.5	2980	2.98	40625	40.625	42.8725	90.2578
16	0.34	85.00	850.0	3792.5	3.7925	42500	42.5	45.48	95.7473



Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 16 hrs but HPMC E4M could not so much control the drug release in 1 hr than formula F13. So further optimization and combination of Polymers required to achieve desired drug release up to 20 hrs.

Conclusion: Tablet was further prepared by using combination of other polymers, optimization of polymer concentration and by changing the method of preparation to achieve desired drug release.

FORMULA- F15:

- Total tablet weight = 250 mg
- Ethyl cellulose: 10%
- Drug: HPMC K1OOM (1:1) (19%)
- Drug: HPC Klucel- HXF (1:1) (19%)

Sr no.	Ingredients	Quantity(mg) (For 1 Tablet)	Quantity(gm) (For 500 Tablets)	Percentage (%)
1	Drug X	47.5	23.75	19.0
2	Ethyl cellulose 45 cps	25	12.5	**10.0**
3	PVP K90 (in water)	6.25	3.125	2.5
4	HPMC K100M	47.5 **(1:1)**	23.75	**19.0**
5	HPC (Klucel - HXF)	47.5 **(1:1)**	23.75	**19.0**
6	PVP K90 (in water)	12.5	6.25	5.0
7	MCC 102	58.75	29.375	23.5
8	Aerosil 200	2.5	1.25	1.0

9	Megnesium stearate	2.5	1.25	1.0
	Total	250	125	100.0

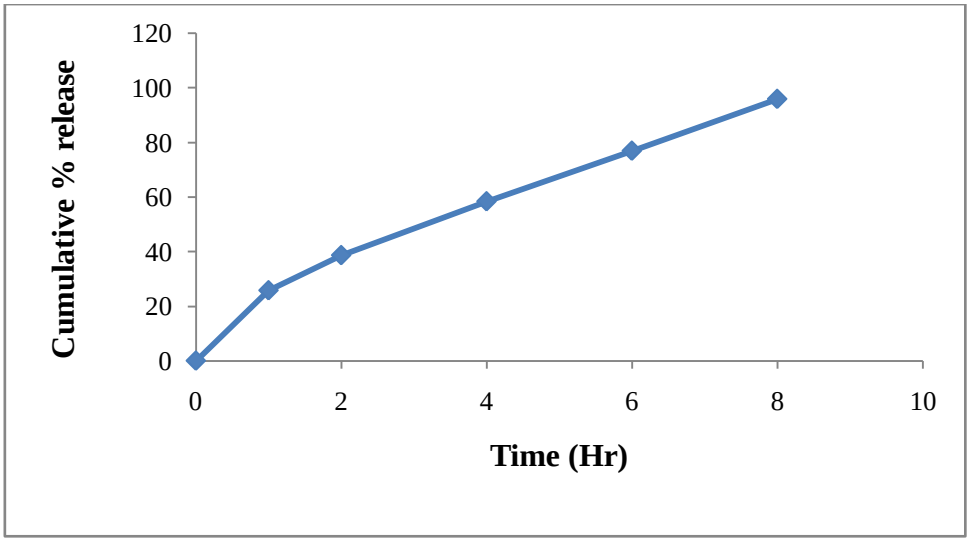
Procedure (Double granulation): First weigh and granulated Drug X and Ethyl cellulose 45 cps using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer and passed dried granules through 24# sieve. Mix HPMC K100M, HPC (Klucel - HXF) and MCC 102 with previous dried granules and then again granulated them using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	**Thickness**	**Friability**	**Cumulative % release**
90-100 N	4.9 mm	0.07%	Nearest to 100% drug release up to 8 hrs.

Cumulative % release:

Time (hr)	**Abs**	**Conc. in µg/ml**	**Conc. in µg/5ml**	**Cumulative conc. (µg)**	**Cumulative conc. (mg)**	**Conc.(µg) in 500ml**	**Conc.(mg) in 500ml**	**Cumulative conc. (mg)**	**Cumulative % release**
0	0	0	0	0	0	0	0	0	0
1	0.098	24.5	122.5	0	0	12250	12.25	12.25	25.7894
2	0.147	36.75	183.7	122.5	0.1225	18375	18.375	18.375	38.6842
4	0.221	55.25	276.2	306.25	0.3062	27625	27.625	27.7475	58.4157
6	0.29	72.5	362.5	582.5	0.5825	36250	36.25	36.5562	76.9605
8	0.36	90.00	450.0	945.0	0.945	45000	45.00	45.5825	95.9631



Result and Discussion: Good result could not get and difficulty in shifting of granules was obtained due to hard granules of water using for both granulation. Nearest to 100 % drug release was achieved in 8 hrs. Optimum Drug release was also not achieved. So the IPA was used instead of water in first granulation to avoid shifting problem and to achieve desired drug release.

Conclusion: Tablet was further prepared by same formula F15 but using IPA instead of water in first granulation for good result and to achieve desired drug release.

FORMULA- F16:

- Total tablet weight = 250 mg
- Ethyl cellulose: 10%
- Drug: HPMC K1OOM (1:1) (19%)
- Drug: HPC Klucel- HXF (1:1) (19%)

Sr no.	Ingredients	Quantity(mg) (For 1 Tablet)	Quantity(gm) (For 500 Tablets)	Percentage (%)
1	Drug X	47.5	23.75	19.0
2	Ethyl cellulose 45 cps	25	12.5	**10.0**
3	PVP K90 (in IPA)	6.25	3.125	2.5
4	HPMC K100M	47.5 **(1:1)**	23.75	**19.0**

5	HPC (Klucel - HXF)	47.5 **(1:1)**	23.75	**19.0**
6	PVP K90 (in water)	12.5	6.25	5.0
7	MCC 102	58.75	29.375	23.5
8	Aerosil 200	2.5	1.25	1.0
9	Megnesium stearate	2.5	1.25	1.0
	Total	250	125	100.0

Procedure (Double granulation): First weigh and granulated Drug X and Ethyl cellulose 45 cps using PVP K90 in IPA as a binder solution. Wet granules were dried in Tray dryer and passed dried granules through 24# sieve. Mix HPMC K100M, HPC (Klucel - HXF) and MCC 102 with previous dried granules and then again granulated them using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

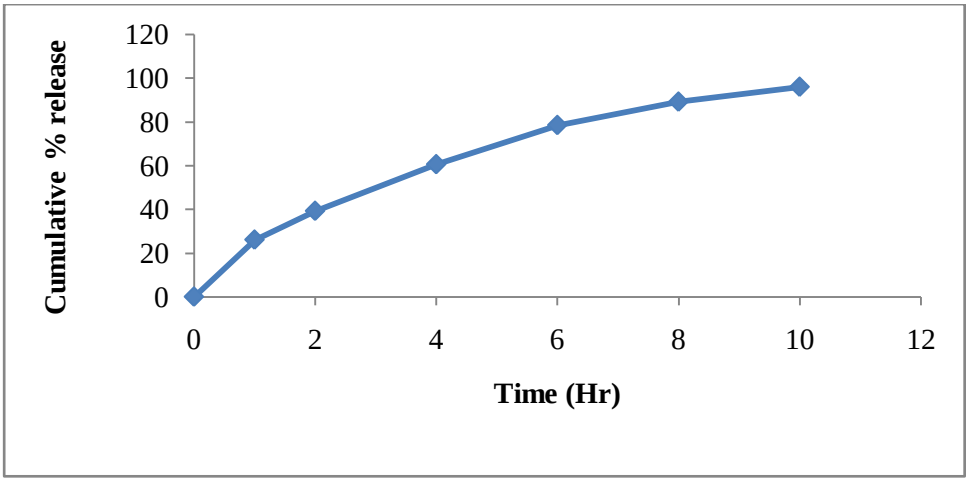
Evaluation:

Hardness	**Thickness**	**Friability**	**Cumulative % release**
90-100 N	4.85 mm	0.06%	Nearest to100% drug release up to 10 hrs.

Cumulative % release:

Time (hr)	**Abs**	**Conc. in µg/ml**	**Conc. in µg/10 ml**	**Cumulative conc. (µg)**	**Cumulative conc. (mg)**	**Conc.(µg) in 500ml**	**Conc.(mg) in 500ml**	**Cumulative conc. (mg)**	**Cumulative % release**
0	0	0	0	0	0	0	0	0	0
1	0.099	24.75	247.5	0	0	12375	12.375	12.375	26.0526
2	0.149	37.25	372.5	247.5	0.2475	18625	18.625	18.625	39.2105
4	0.228	57	570	620	0.62	28500	28.5	28.7475	60.5210
6	0.293	73.25	732.5	1190	1.19	36625	36.625	37.245	78.4105

8	0.329	82.25	822.5	1922.5	1.9225	41125	41.125	42.315	89.0842
10	0.349	87.25	872.5	2745	2.745	43625	43.625	45.5475	95.8894



Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 10 hrs, but so much sticking problem was obtained during granulation and compression. So to avoid this sticking problem, instead of PVP K90 in IPA, only IPA was used in first granulation for next formulation.

Conclusion: Tablet was further prepared by same formula F16 but using only IPA instead of PVP K90 in IPA in first granulation for good result and to achieve desired drug release.

FORMULA- F17:

- Total tablet weight = 250 mg
- Ethyl cellulose: 10%
- Drug: HPMC K1OOM (1:1) (19%)
- Drug: HPC Klucel- HXF (1:1) (19%)

Sr no.	Ingredients	Quantity(mg) (For 1 Tablet)	Quantity(gm) (For 500 Tablets)	Percentage (%)
1	Drug X	47.5	23.75	19.0
2	Ethyl cellulose 45 cps	25	12.5	**10.0**

3	IPA	q.s.	q.s.	
4	HPMC K100M	47.5 **(1:1)**	23.75	**19.0**
5	HPC (Klucel - HXF)	47.5 **(1:1)**	23.75	**19.0**
6	PVP K90 (in water)	12.5	6.25	5.0
7	MCC 102	65	32.5	26.0
8	Aerosil 200	2.5	1.25	1.0
9	Megnesium stearate	2.5	1.25	1.0
	Total	250	125	100.0

Procedure (Double granulation): First weigh and granulated Drug X and Ethyl cellulose 45 cps using IPA as a binder. Wet granules were dried in Tray dryer and passed dried granules through 24# sieve. Mix HPMC K100M, HPC (Klucel - HXF) and MCC 102 with previous dried granules and then again granulated them using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

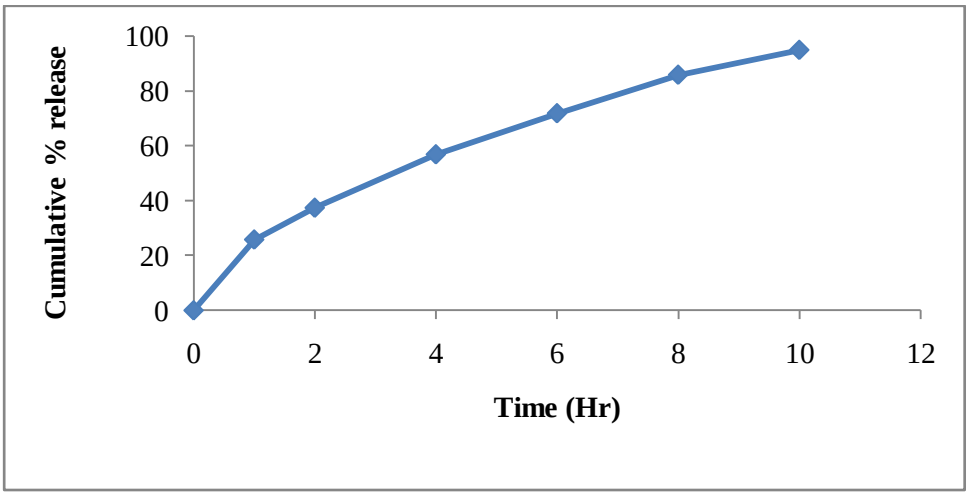
Evaluation:

Hardness	**Thickness**	**Friability**	**Cumulative % release**
90-100 N	4.83 mm	0.06%	Nearest to100% drug release up to 10 hrs.

Cumulative % release:

Time (hr)	**Abs**	**Conc. in µg/ml**	**Conc. in µg/10 ml**	**Cumulative conc. (µg)**	**Cumulative conc. (mg)**	**Conc.(µg) in 500ml**	**Conc.(mg) in 500ml**	**Cumulative conc. (mg)**	**Cumulative % release**
0	0	0	0	0	0	0	0	0	0
1	0.098	24.5	245	0	0	12250	12.25	12.25	25.7894
2	0.142	35.5	355	245	0.245	17750	17.75	17.75	37.3684

4	0.214	53.5	535	600	0.6	26750	26.75	26.995	56.8315
6	0.268	67	670	1135	1.135	33500	33.5	34.1	71.7894
8	0.317	79.25	792.5	1805	1.805	39625	39.625	40.76	85.8105
10	0.346	86.5	865	2597.5	2.5975	43250	43.25	45.055	94.8526



Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 10 hrs. So further optimization of Polymer concentration required to achieve desired drug release up to 20 hrs.

Conclusion: Tablets were further prepared by increasing the concentration of polymers to achieve desired drug release up to 20 hrs.

FORMULA- F18 & F19:

- Total tablet weight = 250 mg
- Ethyl cellulose: 10%, 12%
- HPMC K1OOM: 23%
- Drug: HPC Klucel- HXF (1:1) (19%)

Sr no.	Ingredients	F18	F19

		Quantity(mg) (For 1 Tablet)	**Quantity(mg) (For 1 Tablet)**
1	Drug X	47.5 (19%)	47.5 (19%)
2	Ethyl cellulose 45 cps	25 (10%)	**30 (12%)**
3	IPA	q.s.	q.s.
4	HPMC K100M	**57.5 (23%)**	**57.5 (23%)**
5	HPC (Klucel - HXF)	47.5 (19%)	47.5 (19%)
6	PVP K90 (in water)	12.5 (5%)	12.5 (5%)
7	MCC 102	55 (22%)	50 (20%)
8	Aerosil 200	2.5 (1%)	2.5 (1%)
9	Megnesium stearate	2.5 (1%)	2.5 (1%)
	Total	250	250

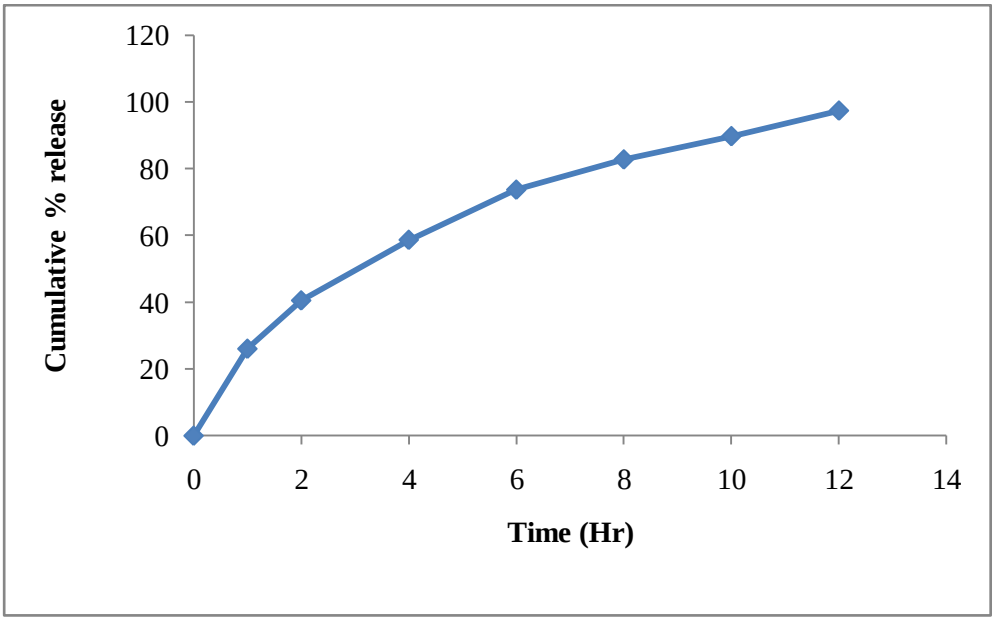
Procedure (Double granulation): First weigh and granulated Drug X and Ethyl cellulose 45 cps using IPA as a binder. Wet granules were dried in Tray dryer and passed dried granules through 24# sieve. Mix HPMC K100M, HPC (Klucel - HXF) and MCC 102 with previous dried granules and then again granulated them using PVP K90 in water as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Parameters	**F18**	**F19**
Hardness	90-100 N	90-100 N
Thickness	4.87	4.89
Friability	0.061%	0.06%
Cumulative % release	Nearest to100% drug release up to 12 hrs.	Nearest to100% drug release up to 18 hrs.

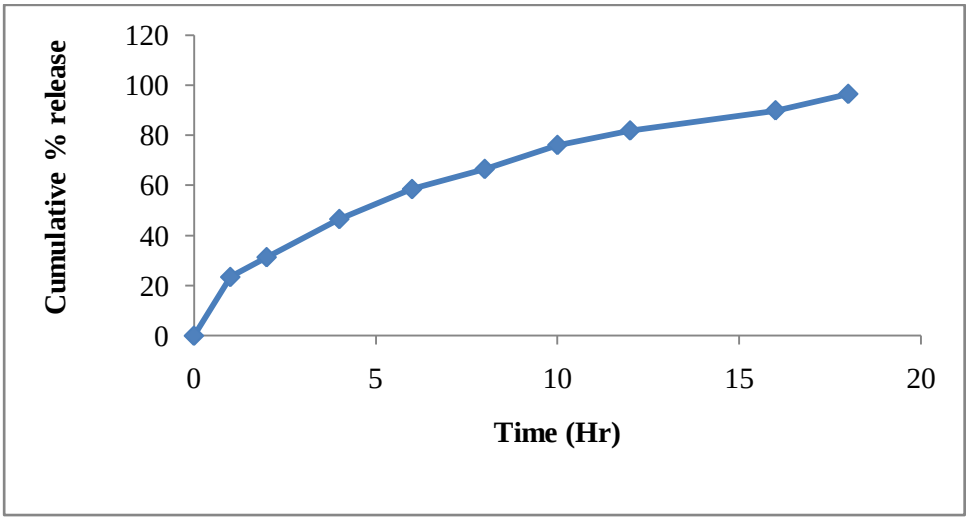
Cumulative % release: F18

Time (hr)	Abs	Conc. in µg/ml	Conc. in µg/10 ml	Cumulative conc. (µg)	Cumulative conc. (mg)	Conc.(µg) in 500ml	Conc.(mg) in 500ml	Cumulative conc. (mg)	Cumulative % release
0	0	0	0	0	0	0	0	0	0
1	0.099	24.75	247.5	0	0	12375	12.375	12.375	26.0526
2	0.154	38.5	385	247.5	0.2475	19250	19.25	19.25	40.5263
4	0.221	55.25	552.5	632.5	0.6325	27625	27.625	27.8725	58.6789
6	0.275	68.75	687.5	1185	1.185	34375	34.375	35.0075	73.7000
8	0.305	76.25	762.5	1872.5	1.8725	38125	38.125	39.31	82.7578
10	0.326	81.5	815	2635	2.635	40750	40.75	42.6225	89.7315
12	0.349	87.25	872.5	3450	3.45	43625	43.625	46.26	97.3894



Cumulative % release: F19

Time (hr)	Abs	Conc. in µg/ml	Conc. in µg/10 ml	Cumulative conc. (µg)	Cumulative conc. (mg)	Conc.(µg) in 500ml	Conc.(mg) in 500ml	Cumulative conc. (mg)	Cumulative % release
0	0	0	0	0	0	0	0	0	0
1	0.089	22.25	222.5	0	0	11125	11.125	11.125	23.4210
2	0.119	29.75	297.5	222.5	0.2225	14875	14.875	14.875	31.3157
4	0.175	43.75	437.5	520	0.52	21875	21.875	22.0975	46.5210
6	0.218	54.5	545	957.5	0.9575	27250	27.25	27.77	58.4631
8	0.245	61.25	612.5	1502.5	1.5025	30625	30.625	31.5825	66.4894
10	0.277	69.25	692.5	2115	2.115	34625	34.625	36.1275	76.0578
12	0.294	73.5	735	2807.5	2.8075	36750	36.75	38.865	81.8210
16	0.319	79.75	797.5	3542.5	3.5425	39875	39.875	42.6825	89.8578
18	0.338	84.5	845	4340	4.34	42250	42.25	45.7925	96.4052



Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 12 hrs for F18 and in 18 hrs for F19. So instead of double granulation, single granulation of F19 was done to achieve desired drug release up to 20 hrs.

Conclusion: Tablets were further prepared by single granulation of F19 instead of double granulation to achieve desired drug release up to 20 hrs.

FORMULA- F20:

- Total tablet weight = 250 mg
- Ethyl cellulose: 12%
- HPMC K1OOM: 23%
- Drug: HPC Klucel- HXF (1:1) (19%)

Sr no.	Ingredients	Quantity(mg) (For 1 Tablet)	Quantity(gm) (For 500 Tablets)	Percentage (%)
1	Drug X	47.5	23.75	19.0
2	Ethyl cellulose 45 cps	30	15	**12.0**
3	HPMC K100M	57.5	28.75	**23.0**
4	HPC (Klucel - HXF)	47.5	23.75	**19.0**
5	PVP K90 (in IPA)	12.5	6.25	5.0
6	MCC 102	50	25	20.0
7	Aerosil 200	2.5	1.25	1.0
8	Megnesium stearate	2.5	1.25	1.0
	Total	250	125	100.0

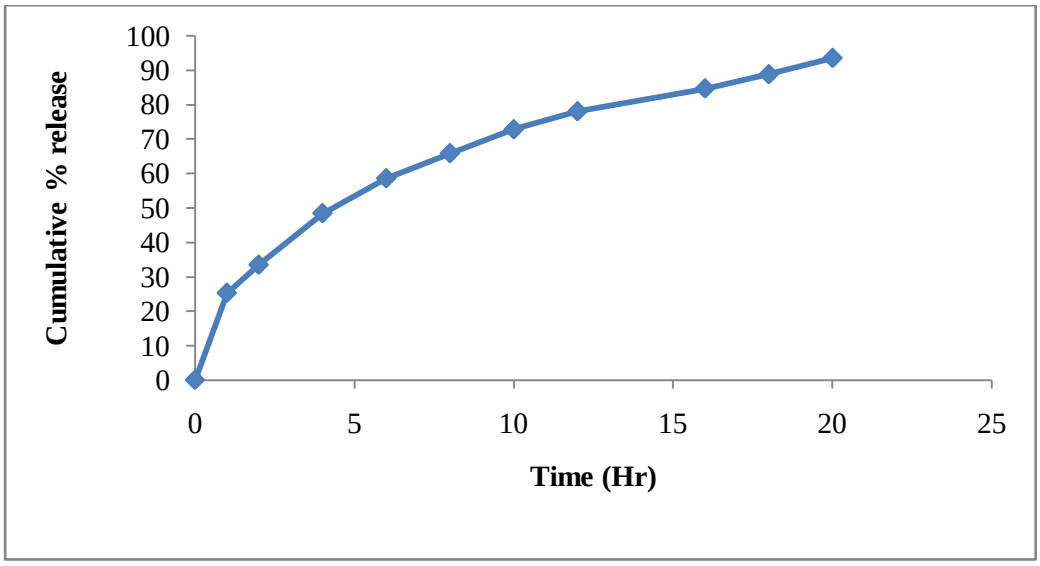
Procedure (Single granulation): First weigh accurate and mix Drug X, Ethyl cellulose 45 cps, HPMC K100M, HPC (Klucel - HXF). They were granulated by Wet granulation method using PVP K90 in IPA as a binder solution. Wet granules were dried in Tray dryer up to LOD (1.5 to 2%) and passed dried granules through 24# sieve. Add MCC 102, Mg stearate and Aerosil 200 extragranularlly. Then Tablet was prepared using 8 station Rotary Tablet Machine (Punch: 8.6 mm, round concave shape) and evaluated for various parameters like Hardness, Thickness, Friability and Cumulative % Release.

Evaluation:

Hardness	Thickness	Friability	Cumulative % release
90-100 N	4.78- 4.8 mm	0.04%	Nearest to100% drug release up to 20 hrs.

Cumulative % release:

Time (hr)	Abs	Conc. in µg/ml	Conc. in µg/10 ml	Cumulative conc. (µg)	Cumulative conc. (mg)	Conc.(µg) in 500ml	Conc.(mg) in 500ml	Cumulative conc. (mg)	Cumulative % release
0	0	0	0	0	0	0	0	0	0
1	0.096	24	240	0	0	12000	12	12	25.2631
2	0.127	31.75	317.5	240	0.24	15875	15.875	15.875	33.4210
4	0.182	45.5	455	557.5	0.5575	22750	22.75	22.99	48.4000
6	0.218	54.5	545	1012.5	1.0125	27250	27.25	27.8075	58.5421
8	0.242	60.5	605	1557.5	1.5575	30250	30.25	31.2625	65.8157
10	0.264	66.0	660	2162.5	2.1625	33000	33.00	34.5575	72.7526
12	0.279	69.75	697.5	2822.5	2.8225	34875	34.875	37.0375	77.9736
16	0.299	74.75	747.5	3520	3.52	37375	37.375	40.1975	84.6263
18	0.309	77.25	772.5	4267.5	4.2675	38625	38.625	42.145	88.7263
20	0.321	80.25	802.5	5040	5.04	40125	40.125	44.3925	93.4578



Result and Discussion: From the above evaluation parameters, it was concluded that nearest to 100 % drug release was achieved in 20 hrs. But to control drug release in starting 1 hr, HPMC K100M CR was used instead of HPMC K100M for next formulation.

Conclusion: Tablets were further prepared by same formula F20 using HPMC K100M CR instead of HPMC K100M and also prepared by using 50% HPMC K100M CR intragranularlly and 50% HPMC K100M CR extragranularlly to control drug release in starting 1 hr.

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