



# Formulation and In-Vitro Evaluation of Controlled Porosity Osmotic Pump Release Tablets of Nifedipine

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**ABSTRACT:** *In this studies, osmotically controlled drug delivery system of Nifedipine using different polymers were formulated. Nifedipine, is an anti-hypertensive drug. It acts as a calcium channel blockers. Unlike any other conventional dosage forms in osmotic system, the mechanism involved is osmosis. In the present studies, the release of the drug is porosity. A total of nine formulations were prepared by using the different polymers (Poly Ethylene oxide, HPMC K15 M and Ethyl cellulose) in different ratios in each formulation were formulated. The tablets were prepared by direct compression method using single station punching machine. The tablets were then dip coated using water soluble coating solvents (cellulose acetate phthalate, PEG, acetone and water). In-vitro studies of controlled release osmotic tablets of nifedipine was carried out.*

**Keywords:-***Nifedipine, osmotic, PEO, HPMC K15 M, EC, PEG.*

## INTRODUCTION

The oral route of drug administration is the most important route of administering drugs for systemic effect. About 90% of drugs used to produce systemic effects are administered by oral route. When a new drug is discovered one of the first questions a pharmacist asks is whether or not the drug can be effectively administered for its intended effect by the oral route.

The drugs that are administered orally, solid oral dosage form represent the preferred class of products. The reasons for this preference are as follows. Tablet is unit dosage form in which one usual dose of the drug has been accurately placed by compression. Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, tablespoon or other measuring device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self administered by the patient<sup>1</sup>.

### Types of tablets:

- a) tablets ingested orally
  1. Compressed tablet, e.g. Paracetamol tablet
    - a. Conventional compressed tablet
    - b. Multiple compressed tablet



2. Repeat action tablets
3. Delayed release tablet, e.g. Enteric coated Bisacodyl tablet
4. Sugar coated tablet, e.g. Multivitamin tablet
5. Film coated tablet, e.g. Metronidazole tablet
6. Chewable tablet, e.g. Antacid tablet

(b) tablets used in oral cavity:

1. Buccal tablet, e.g. Vitamin-C tablet
2. Sublingual tablet, e.g. Vicks Menthol tablet
3. Troches, lozenges or Dental cone

(c) tablets administered by other route:

1. Implantation tablet, e.g. Estradiol
2. Vaginal tablet, e.g. Clotrimazole tablet

(d) tablets used to prepare solution:

1. Effervescent tablet, e.g. Dispirin tablet (Aspirin)
2. Dispensing tablet, e.g. Enzyme tablet (Digiplex)
3. Hypodermic tablet

**Advantages:**

- They are unit dosage forms and they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most compact oral dosage forms.
- They are in general the easiest and cheapest to package.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing and embossed are monogrammed punch face.
- They may provide the greatest ease of swallowing with the least tendency for “hang-up” above the stomach especially when coated provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products such as enteric or delayed release products.
- They are better suited to large scale production than other unit oral forms.



### **Disadvantages:**

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting, dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features may be difficult to formulate and manufacture as a tablet that will still provide adequate full drug bioavailability.
- Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression or the tablets may require coating. In such cases, the tablets may offer the best and lowest cost approach<sup>2</sup>.

### **Tablet properties<sup>3</sup>:**

Tablets can be made in virtually any shape, although requirements of patients and tableting machines mean that most are round, oval or capsule shaped. More unusual shapes have been manufactured but patients find these harder to swallow, and they are more vulnerable to chipping or manufacturing problems.

Tablet diameter and shape are determined by the machine tooling used to produce them - a die plus an upper and a lower punch are required. This is called a station of tooling. The thickness is determined by the amount of tablet material and the position of the punches in relation to each other during compression. Once this is done, we can measure the corresponding pressure applied during compression. The shorter the distance between the punches, thickness, the greater the pressure is applied during compression and sometimes the harder the tablet. Tablets need to be hard enough so that they don't break up in the bottle, yet friable enough that they disintegrate in the gastric tract.

The tablet is composed of the Active Pharmaceutical Ingredient (that is the active drug) together with various excipients. These are biologically inert ingredients which either enhance the therapeutic effect or are necessary to construct the tablet. The filler or diluents (e.g. Lactose or Sorbitol) are a bulking agent, providing a quantity of material which can accurately be formed into a tablet. Binders (e.g. methyl cellulose or gelatin) hold the ingredients together so that they can form a tablet. Lubricants (e.g. magnesium stearate or polyethylene glycol) are added to reduce the friction between the tablet and the punches and dies so that the tablet compression and ejection processes are smooth. Disintegrants (e.g. starch or cellulose) are used to promote wetting and swelling of the tablet so that it breaks up in the gastrointestinal tract; this is necessary to ensure dissolution of the API. Superdisintegrants are sometimes used to greatly speed up the disintegration of the tablet. Additional ingredients may also be added such as coloring agents, flavoring agents and coating agents. Formulations are designed using small quantities in a laboratory machine called a Powder Compaction Simulator. This can prove the manufacturing process and provide information.

### **Choice of excipients<sup>4</sup>:**

The choice of excipients in tablet formulations depends on the API, the type of tablet, the desired characteristics, and the manufacturing process used. Several types of tablets are available in the market. These include prompt release, from which the drug dissolves in a very short time (sublingual or buccal tablets), and immediate release and modified release, which includes most of the oral administered tablets that are swallowed. Other types include effervescent, bilayered, chewable, multiple compressed topical tablets and tablets for solution. The desired characteristics of a tablet may be achieved by adding colors, pigments, flavours, sweeteners and a sugar or film coating. The types of excipients selected for a formulation depend on the basic process used to manufacture the tablets.

### **Drug-excipient interactions and their effect on absorption<sup>5</sup>:**

Excipients are traditionally thought of as inert but they can have tremendous impact on the ultimate pharmacological availability of a drug substance when added to a formulation. The magnitude of this effect will depend on the characteristics of the drug and on the quantity and properties of the excipients. Excipients have



traditionally been classified according to the formulation they perform in a formulation, although many excipients perform multiple functions. Diluents allow the formulation of a practically sized tablet and can form large proportion by weight of a formulated product when, for example, the active ingredient is very potent. The physical characteristics of the diluents are important; for example, triamterene was shown to dissolve more rapidly when it was formulated with hydrophilic fillers such as lactose and starch as compared with insoluble diluents. Disintegrants tend to swell when wetted and so are added to a formulation to facilitate the breakdown of the dosage form into granules and powder particles. The newer disintegrants, called superdisintegrants, cause an extremely rapid break up of a tablet owing to their ability to swell to many times their original size. Wicking and swelling were found to be the primary mechanisms of actions for tablet disintegrants, while other mechanisms, such as deformation recovery, particle repulsion theory, heat of wetting and evolution of a gas etc., may play a role in particular cases of tablet disintegration (Kanig and Rudnic, 1984). Co processing is defined as combining or more established excipients by an appropriate. Coprocessing of excipient could lead to formation of excipients with superior properties compared with the simple physical mixtures of their components or with individual components. A large number of coprocessed diluents are commercially available. The representative examples are Ludipress, Cellactose and starlac. The use of coprocessing is totally unexplored avenues in disintegrants. The widely used super disintegrants are SSG, crospovidone and croscarmellose sodium. Like diluents each super disintegrants have strengths and weakness.

#### **Excipients used in tablets<sup>6</sup>:**

Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch all terms which includes various sub-groups. Comprising diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants or flavours, fragrances and sweeteners. All of these must meet certain criteria as follows:-

1. They must be physiological inert.
2. They must be acceptable to regulatory agencies
3. They must be physiologically and chemically stable.
4. They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
5. They must not interfere with the bioavailability of the drug.
6. They must be commercially available in the form and purity commensurate to pharmaceutical standards.
7. Cost must be relatively inexpensive.
8. They must conform to all current regulatory requirements.

To assure that no excipient interferences with the utilization of the drug, the formulator must carefully and critically evaluate combinations of the drug with each of the contemplated excipients and must ascertain compliance of each ingredient with existing standards and regulations.

The screening of drug-excipients and excipient-excipient interactions should be carried out routinely in preformulation studies.

#### **Fillers: (diluents)**

Tablet fillers comprise of a heterogeneous group of substances. Since they often comprise the bulk of the tablet, selection of a candidate from this group as a carrier for a drug is of prime importance.

E.g.:- Dextrose, lactose, mannitol, MCC, starch, sorbitol, sucrose, DCP, calcium carbonate



### **Binders:**

Binders are the glue that holds powders together to form granules. They are the adhesives that are added to tablet formulations to provide the cohesiveness required for that bonding together of the granules under compaction to form a tablet. The quantity used and the method of application must be carefully regulated, since the tablet must remain intact when swallowed and then release its medicament.

Binders are either sugar or polymeric materials. The latter fall into two classes:

- Natural polymers such as starch or gums (acacia, tragacanth and gelatin).
- Synthetic polymers such as polyvinylpyrrolidone, methyl and ethyl cellulose and hydroxyl propyl cellulose. Binders of both types may be added to the powder mix and the mixture wetted with water, alcohol–water mixtures or a solvent, or binder may be put into solution in the water or solvent and added to the powder. The latter method using the solution of the binder requires much less binding material to achieve the same hardness than if added dry.
- Commonly used binders are gelatin, glucose, methyl cellulose, acacia, starch paste, povidone, alcohol, PVP in water, PVP in alcohol and sorbitol in water

### **Lubricants:**

Lubricants are used in tablet formulation to ease the ejection of the tablet from the die, to prevent sticking of tablets to the punches, and to prevent excessive wear and tear on punches and dies. They function by interposing a film of low shear strength at the interface between the tablet and the die wall and the punch face. Lubricants should be carefully selected for efficiency and for the properties of the tablet formulation.

In selecting a lubricant, the following should be considered:

1. Lubricants markedly reduce the bonding properties of many excipients.
2. Over blending is one of the main causes of lubrication problems. Lubricants should be added last to the granulation and tumble-blended for not more than 10 min.
3. Lubricant efficiency is a function of particle size; therefore, the finest grade available should be used and screened through a 100-300 mesh screen before use.

Examples of lubricants commonly used are magnesium stearate, talc, starch.

### **Disintegrants:**

Disintegrants are used in tablet preparation to break the tablet faster. But some of the disintegrants are also having property of enhancing solubility of insoluble drug.

examples:

- Crospovidone: Crospovidone is disintegrant, crospovidone also enhances solubility.
- Sodium starch glycollate: sodium starch glycollate is widely used in oral pharmaceuticals and as a disintegrant in capsule.



### **Glidants:**

Glidants are materials that improve the flow characteristics of granules by reducing the inter particulate friction. In proper amounts they also serve to assure smooth and uniform flow at all times.

E.g.:- Cab-o-sil, Corn starch

### **Method of preparation of tablet<sup>7</sup>:**

Compressed tablets may be made by three basic methods.

1. Wet granulation
2. Direct compression
3. Dry granulation

### **Controlled release:**

Oral controlled release (CR) systems continue to be the most popular amongst all the drug delivery systems. Because of the pharmaceutical agents can be delivered in a controlled pattern over a long period. Conventional oral drug delivery systems supply an instantaneous release of drug, which cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physico-chemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility etc. To overcome this limitation a number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral dosage form fall in the category of matrix, reservoir or osmotic system. Reservoir systems have a drug core surrounded coated by the rate controlling membrane; there has been increasing interest in the development of osmotic devices over the past 2 decades. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system. the oral osmotic pumps have certainly come a long way and the available products on this technology and number of patent granted in the last few years makes it presence felt in the market. <sup>8,9</sup>

Osmotically Controlled Drug Delivery System (OCDDS), Osmotic devices are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semi permeable membrane coat. <sup>10</sup>

### **advantages<sup>10,11</sup>**

- Easy to formulate and simple in operation.
- Improve patient compliance with reduced frequency.
- Prolonged therapeutic effect with uniform blood concentration.
- They typically give a zero order release profile after an initial lag.
- Deliveries may be delayed or pulsed if desired.
- Drug release is independent of gastric pH and hydrodynamic condition.
- They are well characterized and understood.
- The release mechanisms are not dependent on drug.
- A high degree of in-vitro and in-vivo correlation (IVIVC) is obtained in osmotic systems.
- The rationale for this approach is that the presence of water in git is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.



- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

#### Disadvantages<sup>10, 11</sup>

- Dose dumping.
- Rapid development of tolerance.
- Retrieval therapy is not possible in the case of unexpected adverse events.
- Expensive.
- If the coating process is not well controlled there is a risk of film defects, which results in dose dumping.
- Size hole is critical.

#### Osmosis and its principle<sup>8</sup>

Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Conventionally, osmosis can be defined as the net movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane that allows passage of water but cast offs solute molecules or ions . The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. He showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature. In 1886, Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature. He revealed that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation.

$$\Pi = \emptyset c RT$$

Where,

$\Pi$  = Osmotic pressure,

$\emptyset$  = osmotic coefficient,

c = molar concentration,

R = gas constant,

T = Absolute temperature.

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug.



### Classification of osmotic drug delivery system

- A. Implantable<sup>11</sup>
  - 1. The Rose and Nelson Pump
  - 2. Higuchi Leeper Pump
  - 3. Higuchi Theuwes pump
  - 4. Implantable Mini osmotic pump
- B. Oral osmotic Pump<sup>11</sup>
  - I. Single chamber osmotic pump:
    - 1. Elementary osmotic pump
  - II. Multi chamber osmotic pump:
    - 1. Push pull osmotic pump,
    - 2. Osmotic pump with non expanding second chamber
  - III. Specific types:
    - 1. Controlled porosity osmotic pump,
    - 2. Liquid OROS,
    - 3. Delayed Delivery Osmotic device,
    - 4. Telescopic capsule,
    - 5. OROS-CT (colon targeting),
    - 6. Sandwiched oral therapeutic system,
    - 7. Lipid osmotic pump
    - 8. Multiparticulate osmotic pump
    - 9. Monolithic osmotic system
    - 10. OSMAT.

#### A. Implantable

##### 1. Rose and nelson pump:

Rose and Nelson were two Australian physiologists interested in the delivery of drugs to the gut of sheep and cattle. Their pump was never patented. The pump consisted of three chambers: a drug chamber, a salt chamber containing excess solid salt, and a water chamber. The drug and water chambers are separated by a rigid semi permeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. The volume of the salt chamber increases because of the water flow, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device. The pumping rate of the Rose-Nelson pump is given by the Equation

$$dM_t/dt = (dv/dt) C \dots\dots\dots (1)$$

Where,  $dM_t/dt$  is the drug release rate,  $dv/dt$  is the volume flow of water in to salt chamber and  $C$  is the concentration of drug in the drug chamber.<sup>12</sup>

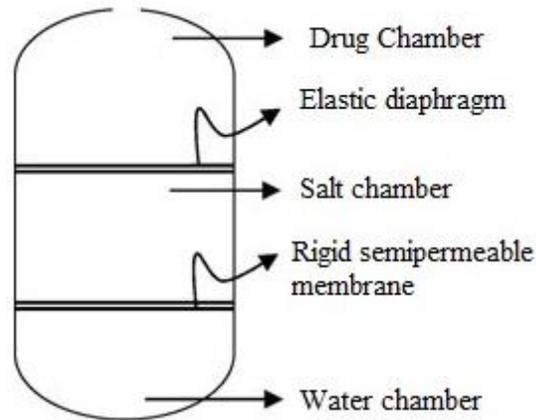


figure 1. rose-nelson pump

In general, this equation, with or without some modifications, applies to all other type of osmotic. Several simplifications in Rose-Nelson pump were made by Alza Corporation in early 1970s. The Higuchi-Leeper pump is modified version of RoseNelson pump.

## 2. Higuchi leeper pump:

Higuchi Leeper pump is widely used for veterinary use. This type of pump is either swallowed or implanted in the body of animal for delivery of antibiotic or growth hormones. Higuchi Leeper pump consist of rigid housing and semi permeable membrane. A layer of low melting waxy solid, such as microcrystalline paraffin wax is used in place of elastic diaphragm to separate the drug and osmotic chamber. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug.<sup>8</sup>

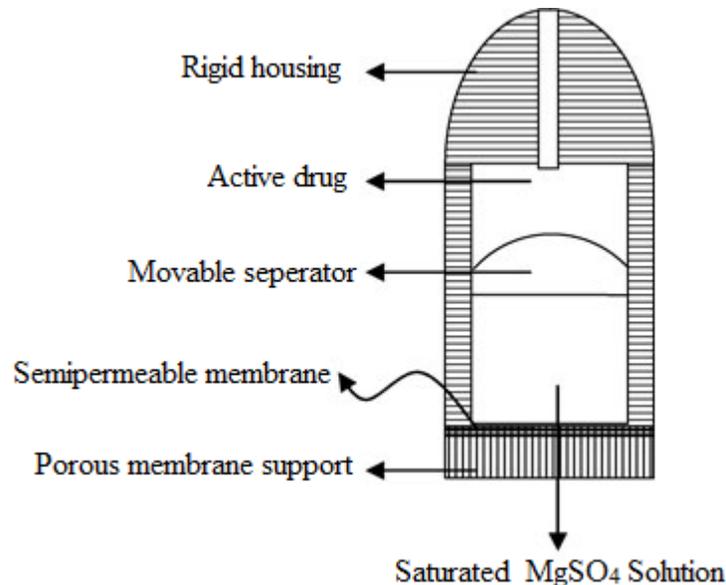


figure 2: higuchi leeper pump



### 3. Higuchi theuwes pump:

Higuchi Theuwes pump is illustrated in figure 3 in this device the rigid housing is made up of semi permeable membrane which is enough strong to withstand with the pumping pressure developed inside the device due to permeation of water. The drug is loaded only to the prior of application of device. The release of drug from device can be controlled by salt used in chamber, the permeability characteristic of outer membrane and orifice. Osmotic pump of this form are available under trade name Alzet. A mixture of citric acid and sodium bi carbonate in salt chamber in presence of water generate carbon dioxide gas. Which exert a pressure on the elastic diaphragm, eventually delivers the drug from device.<sup>8</sup>

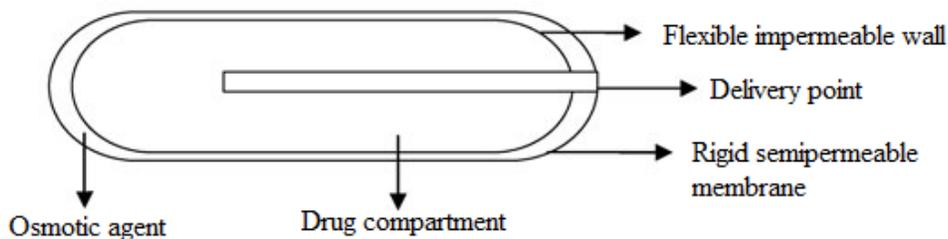


Figure 3: Higuchi Theuwes Pump

### 4. Implantable mini osmotic pump:

Implantable Mini osmotic pump shown in figure 4, is composed of three concentric layers-the drug reservoir, the osmotic sleeves and the rate controlling semi permeable membrane. The additional component called flow moderator is inserted into the body of the osmotic. The inner most compartment of drug reservoir which is surrounded by an osmotic sleeve, a cylinder containing high concentration of osmotic agent. The osmotic sleeve is covered by a semi permeable membrane when the system is placed in aqueous environment water enters the sleeve through semi permeable membrane, compresses the flexible drug reservoir and displaces the drug solution through the flow moderator. These pumps are available with variety of delivery rates between 0.25 to 10ml per hour and delivery duration between one day and four weeks.<sup>8</sup>

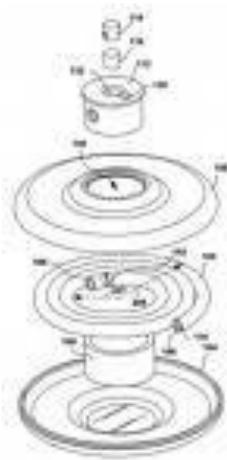


figure 4: implantable osmotic pump



## B. Oral osmotic Pump<sup>11</sup>

### Single chamber osmotic pump

#### 1. Elementary osmotic pump(eop):

Elementary osmotic pump works on the same mechanism as the implantable pumps it is simplest possible form of osmotic pump as it does not require special equipment and technology. This device was further simplification of Higuchi – Theeuwes pump. It was developed in the year 1975 by Theeuwes (Santus et al,1995) The EOP consist of single layered tablet core containing a water soluble drug with or without other osmotic agent .A semi permeable membrane surrounds the tablet core. When such a system is swallowed, water from the GIT enter through the membrane in the core, the drug dissolved and the drug solution is pumped out through the exit orifice. This process continues at a constant rate until the entire solid drug inside the tablet has been dissolved drug continues to be delivered but at a declining rate until the osmotic pressure between outside environment and saturated drug solution. Normally the EOP delivers 60 - 80% of its content at a constant rate and there is a short lag time of 30- 60 min as the system hydrates before zero order drug release from the EOP is obtained.<sup>11,13</sup>

#### ii. Multi chamber osmotic pump:

##### 1. Push pull osmotic pump

Push pull osmotic pump is a modified EOP (Vyas et al, 2001; Barclay et al, 1987) through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (depict as the upper layer) contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and colouring agents, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semi permeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet.<sup>11</sup>

##### 2. Osmotic pump with non expanding second chamber

The second category of multi-chamber devices comprises system containing a non-expanding second chamber. This group can be divided into two sub groups, depending on the function of second chamber. In one category of these devices, the second chamber is used to dilute the drug solution leaving the devices. This is useful because in some cases if the drug leaves the oral osmotic devices a saturated solution, irritation of GI tract is a risk. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. In use water is drawn into both the chamber through the surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs.<sup>11</sup>

#### iii. Specific types

##### 1. Controlled porosity osmotic pump

The controlled-porosity osmotic pump tablet concept was developed as an oral drug delivery system by Zentner et al (1985, 1991), Zentner and Rork (1990), Appel and Zentner (1991), and Mc Celland et al. (1991). The controlled-porosity osmotic pump tablet (CPOP) is a spray-coated or coated tablet with a semi permeable membrane (SPM) containing leachable pore forming agents. They do not have any aperture to release the drugs; drug release is achieved through the pores, which are formed in the semi permeable wall in situ during the operation. In this system, the drug, after dissolution inside the core, is released from the osmotic pump tablet by hydrostatic pressure and



diffusion through pores created by the dissolution of pore formers incorporated in the membrane (Figure 5). The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by a tablet component, after water is imbibed across the semi permeable membrane.<sup>10, 14</sup>

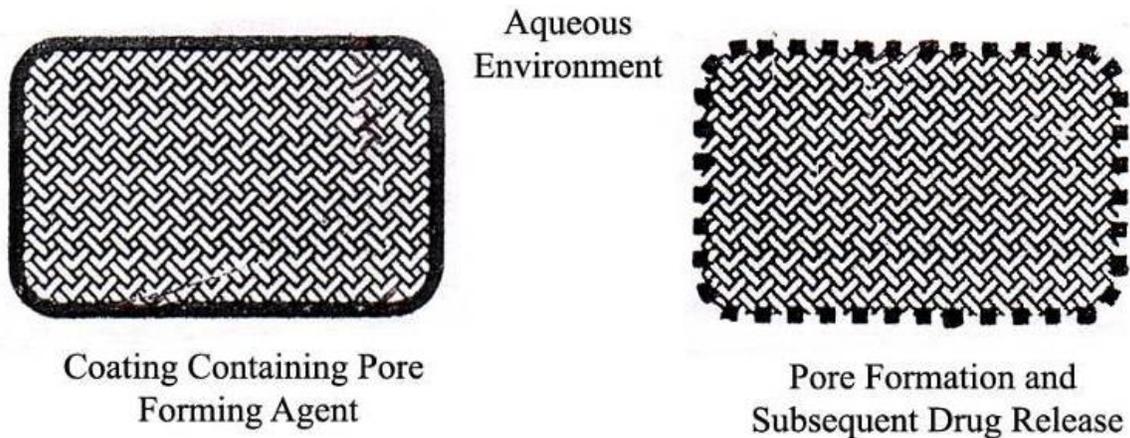


figure 5: cpop tablet before and after dissolution studies

## 2. Liquid oros<sup>4</sup>

Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of three types

- L OROS hard cap,
- L OROS soft cap,
- Delayed liquid bolus delivery system

## 3. Delayed delivery osmotic device

Because of their semi permeable walls, an osmotic device inherently show lag time before drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously. The delayed release of certain drug (drugs for early morning asthma or arthritis) may be beneficial. The following text describe other means to further delay drug release.<sup>11</sup>

## 4. Telescopic capsule for delayed release

This device consists of two chambers, the first contains the drug and an exit port, and the second contains an osmotic engine. A layer of wax like material separates the two sections. To assemble the delivery device, the desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections.<sup>11</sup>



## 5. Oros-ct (colon targeting)

OROS-CT (Alza corporation) is used as a once or twice a day formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it can be comprised of as many as five to six push pull osmotic unit filled in a hard gelatin capsule. After coming in contact with the gastric fluids, gelatin capsule dissolved and the enteric coating prevents entry of fluids from stomach to the system as the system enters into the small intestine the enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell. At the same time flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate, which is precisely controlled, by the rate of water transport across the semi permeable membrane.<sup>15</sup>

## 6. Sandwiched oral therapeutic system

It is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment. The middle push layer containing the swelling agents, swells and the drug is released from the delivery orifices. The advantage of this type of system is that the drug is released from the two orifices situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.<sup>11,16</sup>

## 7. Lipid osmotic pump

Merk describes an osmotic pump for the lipid delivery as shown in the figure. The device concerns an osmotic agent for dispensing beneficial active agent that has poor solubility in water. The core of the system comprises a beneficial amount of a substantially water- insoluble active agent, which is lipid soluble or lipid- wettable; a sufficient amount of water insoluble lipid carrier, which is liquid at the temperature of use to dissolve or suspend the drug and agent to ensure the release of the lipid carrier of the drug from the pump (God billion et al, 1985) The water insoluble wall is micro porous and is wetted by lipid carrier. The device is prepared by first dissolving the drug of interest in the lipid vehicle. The osmogent (Sodium chloride) is dispersed in the melted lipid and then quenched-cool to form a lump that are broken and made into tablet. The micro porous is coated at a moderate flow of unheated ambient air.<sup>14</sup>

## 8. Multiparticulate osmotic pump

MPOP consist of pellets comprises of drug with or without osmotic agent, which are coated with a semipermeable membrane. When this system comes in contact with the aqueous environment, water penetrates in the core and forms a saturated solution of soluble component (Schultzew et al, 1997). The osmotic pressure difference results in rapid expansion of the membrane, leading to the formation of pores. The osmotic agent and the drug released through the pores according to zero order kinetics. The lag time and dissolution rate were found to be dependent on the coating level and the osmotic properties of the dissolution medium.<sup>15</sup>

## 9. Monolithic osmotic system

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact in with the aqueous environment water imbibitions by the active agents takes place rupturing the polymer matrix capsule surrounding the drug, thus liberating it to the outside environment (Mishra et al, 2006). Initially this process occurs at the outer environment of the polymeric matrix, but gradually proceeds towards the interior of the matrix in a serial fashion. However this system fails if more than 20 –30 volume per liter of the active agents is incorporated in to the device as above this level, significant contribution from the simple leaching of the substance take place.<sup>11,17</sup>

## 10. Osmat

It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semipermeable membrane in-situ releases from such a matrix system containing an



osmogen could, therefore be modulated by the osmotic phenomenon. Osmat thus judiciously combines both matrix osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix system. Osmat produces controlled drug release with adequate delivery rates in an agitation in dependent manner. Thus osmat represents simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cost technology.<sup>11</sup>

### **Basic components of osmotic systems<sup>8</sup>**

#### **Drug**

All drugs are not suitable candidate for osmotic system as prolong action medication. Drug with biological half life  $> 12$  hr e.g.: Diazepam and drug which have very short half life i.e.  $< 1$  hr e.g. Penicillin G, furosemide are not suitable candidate for osmotic controlled release. Drug which have biological half-life in between 1 – 6 hrs and which is used for prolonged cure of diseases are ideal applicant for osmotic systems. A variety of drug candidates such as Diltiazem HCl<sup>32</sup>, Carbamazepine, Metoprolol<sup>33</sup>, Oxprenolol, Nifedipine<sup>34</sup>, Glipizide<sup>35</sup> etc. are formulated as osmotic delivery.

#### **Semi permeable membrane<sup>21,22</sup>**

There are various types of polymers are used as semi permeable membrane. The selection of polymer is based on the solubility of drug as well as amount and rate of drug to be released from pump. Cellulose acetate is commonly used polymer for preparation of semi permeable for osmotic pump devices. Different grades of cellulose acetate with different acetyl content usually 32% and 38% are mostly used. Apart from cellulose derivative, some other polymers such as poly (vinyl methyl) ether copolymer, poly (orthoester), poly acetals and selectively permeable poly(glycolic acid) and poly(lactic acid) derivatives, Eudragit can be used as semi permeable film forming materials. The permeability is the most important criteria for the selection of semi permeable membrane. Therefore, the polymeric membrane selection is important to osmotic delivery formulation. The membrane must have certain performance criteria such as:

- It should be adequately thick to withstand the pressure generated within the device.
- It should have enough wet strength and water permeability
- It should be biocompatible.
- It should be rigid and non-swelling

The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.

#### **Plasticizers**

Plasticizers have a crucial role to play in the formation of a film coating and its ultimate structure. Plasticizer increases the workability, flexibility and permeability of fluids. Generally from 0.001 to 50 parts of plasticizer or a mixture of plasticizers are incorporated in to 100 part of wall forming material. They can change viscous-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Plasticizers can have a marked effect both quantitatively and qualitatively on the release of active materials from modified release dosage forms where they are incorporated into the rate-controlling membrane<sup>36</sup>. Some of the plasticizers used are as: Polyethylene glycols, Glycolate, Glycerolate, myristates, Ethylene glycol monoacetate; and diacetate- for low permeability, Tri ethyl citrate, Diethyl tartarate or Diacetin- for more permeable films.



### **Osmotic agent**<sup>10, 20, 21</sup>

Osmogent are essential ingredient of osmotic pump, usually it is an ionic compound consisting of either inorganic salts or hydrophilic polymers and carbohydrates. Generally combination of osmogent is used to achieve desired osmotic pressure within the device. Some of the osmotic agents that can be used for such systems are classified below.

- Inorganic water-soluble osmogents: Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassium chloride, Sodium bicarbonate
- Organic polymer osmogents: Sodium carboxy methyl cellulose, Hydroxy propyl methyl cellulose, Hydroxyethylmethylcellulose, Methylcellulose, Polyethylene oxide, polyvinyl pyrrolidone.

### **Wicking agent**

The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent help to enhance the rate of drug released from the orifice of the drug. The examples are colloidal silicon dioxide, PVP & Sodium lauryl sulphate.

### **Pore former**<sup>22</sup>

These agents are particularly used in the development of pump for poorly water soluble drugs and in controlled porosity tablets. These agents cause the formation of micro porous membrane. The micro porous wall may be formed by the leaching of water soluble substrate from membrane leaving a micro porous structure. The pore former can be organic or inorganic and solid or liquid in nature. Some examples of pore former are given below. Alkaline earth metal salts: Sodium chloride, potassium chloride, sodium bromide, potassium phosphate. Carbohydrate such as sucrose, lactose, glucose, mannitol, fructose etc is used as pore forming agent.

### **Coating solvents**<sup>23</sup>

The primary function of solvent system is to dissolved or dispersed the polymer and other additive and convey them to substrate surface. Solvent used to prepare polymeric solution include inert inorganic and organic solvents that do not adversely harm the core ,wall and other material .the various types of solvents and their combinations are as follows: Methylene chloride, methanol, isopropyl alcohol, di-chloromethane , ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, water etc and the mixture of solvents such as acetone-methanol(80:20), methylene chloride- methanol(79:21),acetone-ethanol(80:20), methylene chloride-methanol-water (75:22:3).

The ideal solvent system should have following properties.

- It should easily and completely dissolve the polymer.
- It should easily disperse other coating components into solvent system.
- It should not give extremely viscous solution with Small concentration of polymer (2-10%) because it create process problem.
- It should be odorless, colorless, tasteless, inexpensive, nontoxic and non-irritant.
- It should have rapid drying rate.

### **Factors affecting drug release rate**<sup>24, 25</sup>

Solubility: APIs for osmotic delivery should have water solubility in the desired range to get optimize drug release. However, by modulating the solubility of these drugs within the core, effective release patterns may be obtained for the drugs, which might otherwise appear to be poor candidate for osmotic delivery.



### Solubility-modifying approaches

- *Use of swellable polymers:* Vinyl Acetate Copolymer, Polyethylene Oxide have uniform swelling rate which causes drug release at constant rate.
- *Use of wicking agents:* These agents may enhance the surface area of drug with the incoming aqueous fluids. e.g. Colloidal Silicon Dioxide, Sodium Lauryl Sulfate, etc. Ensotrol® technology uses the same principle to deliver drugs via osmotic mechanism.
- *Use of effervescent mixtures:* Mixture of citric acid and sodium bicarbonate which creates pressures in the osmotic system and ultimately controls the release rate.
- *Use of Cyclodextrin derivatives:* They are known to increase solubility of poorly soluble drugs. The same phenomenon can also be used for the osmotic systems.
- *Use of alternative salt form:* Change in salt form of may change solubility.
- *Use of encapsulated excipients:* Solubility modifier excipient used in form of mini-tablet coated with rate controlling membrane.
- *Resin Modulation approach:* Ion-exchange resin methods are commonly used to modify the solubility of APIs. Some of the resins used in osmotic systems are Poly (4-Vinyl Pyridine), Pentaerythritol, Citric and Adipic Acids.
- *Use of crystal habit modifiers:* Different crystal form of the drug may have different solubility, so the excipient which may change crystal habit of the drug can be used to modulate solubility. Co-compression of drug with excipients: Different excipients can be used to modulate the solubility of APIs with different mechanisms like saturation solubility, pH dependent solubility. Examples of such excipients are Organic acids, Buffering agent, etc.

### Osmotic pressure

The next release-controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment.

The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment.

**The following table shows osmotic pressure of commonly used solutes in cr formulations.**

Compound or mixture	Osmotic pump atmospheric pressure
Sodium chloride	356
Potassium chloride	245
Fructose	355
Sucrose	150
Dextrose	82
Potassium sulphate	39
Mannitol	38
Lactose-fructose	500
Dextrose-fructose	450
Sucrose-fructose	430
Mannitol-fructose	415
Lactose-sucrose	250
Lactose-dextrose	225
Mannitol-dextrose	225



### Size of delivery orifice

To achieve an optimal zero order delivery profile, the cross sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure build up in the system. The typical orifice size in osmotic pumps ranges from 600 $\mu$  to 1 mm.

Methods to create a delivery orifice in the osmotic tablet coating are

- Mechanical drill
- Laser drill: This technology is well established for producing sub-millimeter size hole in tablets. Normally, CO<sub>2</sub> laser beam (with output wavelength of 10.6 $\mu$ ) is used for drilling purpose, which offers excellent reliability characteristics at low costs.
- Indentation that is not covered during the coating process: Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.
- Use of leachable substances in the semi-permeable coating: e.g. controlled porosity osmotic pump

### Aim and objective

The aim of the work is to investigate the possibility of obtaining a prolonged, relatively constant level of Nifedipine. Nifedipine which is an antihypertensive drug has poor aqueous solubility, short half life and undergo an excessive first pass metabolism. So it is prescribed 2-3 times/day for the treatment of hypertension which leads to poor patient compliance and development of tolerance. Present studies investigate the possibility for the development of Osmotic tablet of Nifedipine, to reduce the side effect, dosing frequency and improve patient compliance.

### Materials and methods

**Table 1: List of Materials and Suppliers**

S.NO.	Ingredients	Supplier
1.	Nifedipine	Supplied By Pharma Train
2.	Poly Ethylene Oxide	SD Fine Chemicals, Mumbai
3.	HPMC K 15 M	SD Fine Chemicals, Mumbai
4.	Ethylcellulose N50	SD Fine Chemicals, Mumbai
5.	Mannitol	SD Fine Chemicals, Mumbai



6.	Cros Carmellose Sodium	SD Fine Chemicals, Mumbai
7.	Magnesium Stearate	SD Fine Chemicals, Mumbai

**Table 2: List of equipments and Companies**

S. No.	Name of the Equipment	Model
1.	Electronic weighing balance	Scale-tec
2.	Friabilator	Roche Friabilator Electrolab, Mumbai
3.	Laboratory oven	Dtc-00r
4.	Compression machine	Cmd(Cadmach)
6.	Tablet hardness tester	Pfizer Hardness Tester, Mumbai
7.	UV	Labindia Uv 3000+
8.	Dissolution apparatus	Electrolab TDT-08L
9.	Vernier calipers	Cd-6”Cs

### I. Analytical Method Development

#### Preparation of 0.1 N Hydrochloric Acid (P<sup>H</sup> 1.2) with 0.5% SLS

8.5 ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000 ml. Then add and dissolve 5gm of sodium lauryl sulphate in same solution.

#### Determination of Nifedipine $\lambda_{max}$ in 0.1N HCL with 0.5% SLS

##### Procedure:

**Working standard:** 100mg of Nifedipine was weighed and dissolved in 10ml methanol and then make up to the volume with 0.1N HCL with 0.5% SLS, it give 1000 $\mu$ g/ml concentrated stock solution.

**Dilution 1:** From the working standard, 10ml solution was diluted to 100ml with 0.1NHCL with 0.5% SLS, it will give 100 $\mu$ g/ml concentrated solution.

**Dilution 2:** From the dilution1, 10ml solution was diluted to 100ml with 0.1NHCL with 0.5% SLS, it will give 10 $\mu$ g/ml concentrated solutions.

This solutions was scanned at range of 200-400nm wavelength light corresponding scan spectrum curve was noted. The corresponding wavelength having highest absorbance is noted as  $\lambda_{max}$



### Construction of calibration curve of Nifedipine in 0.1N HCL with 0.5% SLS

#### Procedure:

**Working standard:** 100mg of Nifedipine was weighed and dissolved in 10ml methanol and then make up to the volume with 0.1NHCL with 0.5% SLS, it give 1000µg/ml concentrated stock solution.

**Dilution 1:** From the working standard, 10ml solution was diluted to 100ml with 0.1NHCL with 0.5% SLS, it will give 100 µg/ml concentrated solutions.

**Dilution 2:** From dilution 1, take 0.2, 0.4, 0.6, 0.8, and 1ml of solution was diluted up to the mark with 0.1NHCL with 0.5% SLS in 10ml volumetric flask to obtain 2, 4, 6, 8 and 10µg/ml concentrated solutions. This solutions absorbance was noted at 241nm.

### II. Preparation of core tablets

#### Procedure

Accurately weighed quantities of ingredients mentioned in formula were passed through sieve no.80. The entire ingredients, except lubricant (magnesium stearate) were manually blended homogeneously in a motor by geometric dilution. Finally blended with magnesium stearate. The homogeneous blend was then compressed into tablets by using concave punches. The compression was adjusted to tablet with approximately 7-8 kg cm<sup>2</sup> hardness.

Table 3: Formulation for Nifedipine Osmotic pump tablets

Ingredients	Formulation code								
	1	2	3	4	5	6	7	8	9
Nifedipine	30	30	30	30	30	30	30	30	30
Poly ethylene oxide	10	20	30	-	-	-	-	-	-
HPMC K15M	-	-	-	10	20	30	-	-	-
Ethylcellulose N50	-	-	-	-	-	-	10	20	30
Mannitol	177	167	157	177	167	157	177	167	157
CCS	10	10	10	10	10	10	10	10	10
Mg.stearate	3	3	3	3	3	3	3	3	3
Total wt (mg)	230	230	230	230	230	230	230	230	230



### Coating of tablet

The tablet coatings were applied using dip coating process. The tablets were dip coated in polymer solution consisting of CAP (cellulose acetate phthalate) dissolved in solutions of acetone, water and PEG. In this, cores to be dipped into coating solution and then dried taking care to prevent adherence to one another. For obtaining more perfect or heavier coats the dipping and drying steps repeated several times one after another.

**Table 4: Preparation of Coating solution**

Ingredients	Quantity
Cellulose acetate phthalate	4mg
PEG	0.5ml
Acetone	10ml
Water	1ml

## RESULTS AND DISCUSSION

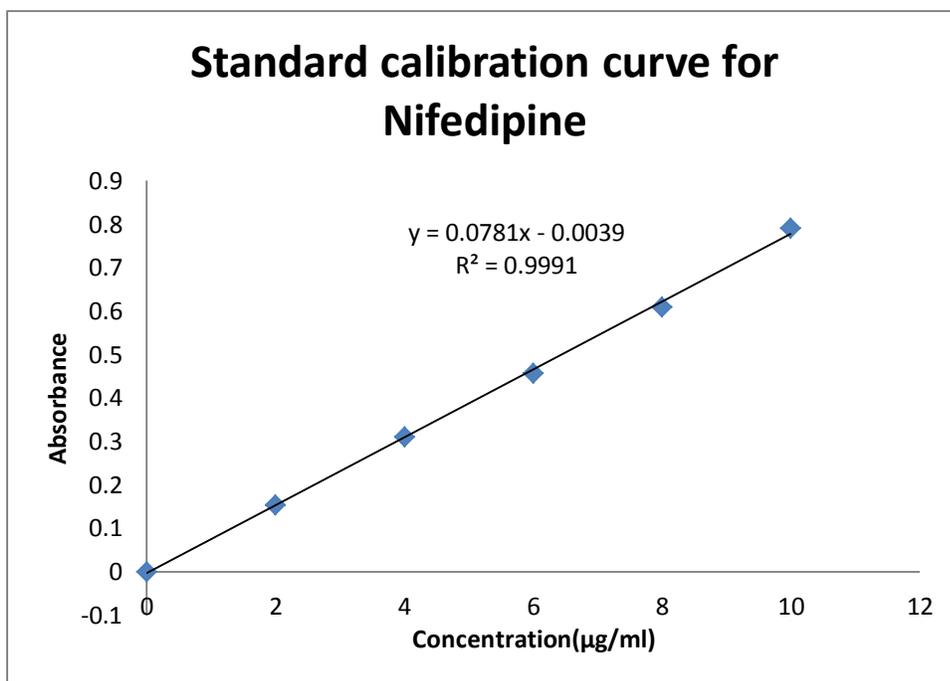
### 1. Construction of Standard calibration curve of Nifedipine in 0.1N HCL with 0.5% SLS:

The absorbance of the solution was measured at 241nm, using UV spectrometer with **0.1N HCL with 0.5% SLS** as blank. The values are shown in below table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10  $\mu\text{g/ml}$ .

**Table 5: Standard Calibration graph values of Nifedipine in 0.1N HCL with 0.5% SLS at 241 nm**

Concentration ( $\mu\text{g} / \text{ml}$ )	Absorbance at 241 nm
0	0
2	0.153
4	0.310
6	0.457
8	0.609
10	0.790

Standard plot of Nifedipine is plotted by taking absorbance on Y – axis and concentration ( $\mu\text{g/ml}$ ) on X – axis, the plot is shown in below figure.



**Figure 6: Standard calibration curve of Nifedipine in 0.1N HCL with 0.5% SLS at 241nm**

**Inference:** The standard calibration curve of Nifedipine in 0.1N HCL with 0.5% SLS showed good correlation with regression value of 0.999

## 2. Evaluation of Tablets:

### A) Pre Compression studies:

**Table 6: Pre compression studies for Nifedipine tablets**

Formulation Code	Bulk density	Tapped density	Cars index	Hausners ratio	Angle of repose
F1	0.54	0.61	11.47	1.12	31.26
F2	0.52	0.59	11.86	1.13	32.31
F3	0.45	0.50	10.00	1.11	30.42
F4	0.44	0.51	13.72	1.15	33.81
F5	0.4	0.45	11.11	1.12	32.14
F6	0.48	0.55	12.72	1.14	34.38
F7	0.50	0.56	10.71	1.12	31.75
F8	0.45	0.53	15.09	1.17	37.83
F9	0.46	0.51	09.80	1.10	29.32



**Inference:**

- Nifedipine tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of  $\leq 18$  and 1.10 to 1.17 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 29.32-37.83° which indicating passable flow.

**B) Post compression studies:**

**Table 7: Post compression studies of Nifedipine tablets**

Formulation Code	% Weight Variation	Thickness (mm)	% Friability	% Drug Content	Hardness (Kg/cm <sup>2</sup> )
F1	pass	4.92	0.120	101.2	7.69
F2	pass	5.12	0.312	101.5	7.43
F3	pass	5.02	0.13	99.2	7.69
F4	pass	5.02	0.123	99.9	7.48
F5	pass	4.93	0.110	100.2	7.7
F6	pass	5.10	0.133	100.5	7.53
F7	pass	5.03	0.132	99.6	7.63
F8	pass	5.03	0.143	98.9	7.5
F9	pass	5.03	0.62	100.1	7.85

\*Test for Friability was performed on single batch of 20 tablets

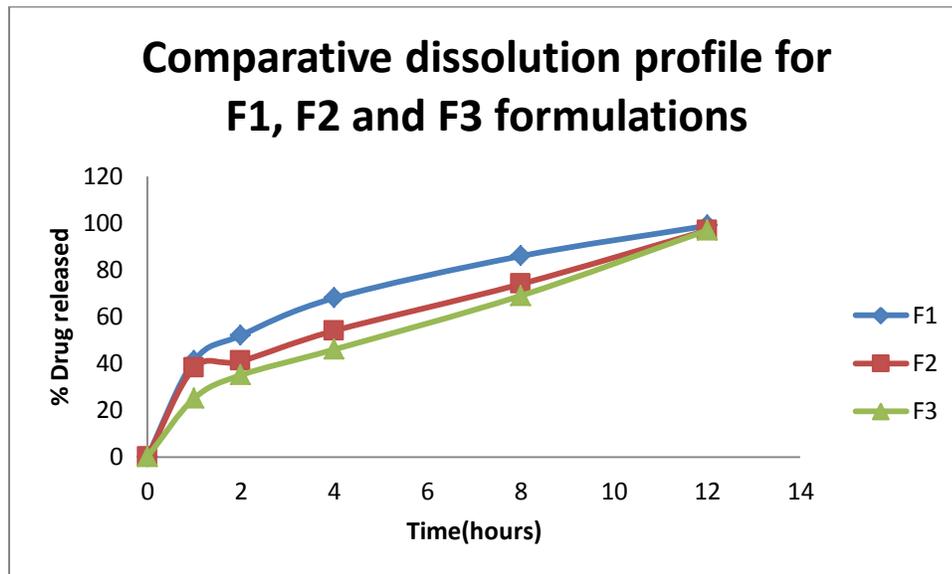
**Inference:**

- The variation in weight was within the limit.
- The thickness of tablets was found to be between 4.92 – 5.12 mm.
- The hardness for different formulations was found to be between 7.48 to 7.85 kg/cm<sup>2</sup>, indicating satisfactory mechanical strength.
- The friability was  $< 1.0\%$  W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 102 %.



**Table 8: In-vitro Dissolution results of Formulation trails**

Time (Hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	41	38	25	21	11	7	11	7	6
2	52	41	35	32	26	11	24	22	12
4	68	54	46	53	46	33	40	38	27
8	86	74	69	74	68	53	60	59	43
12	99	97	97	98	89	78	75	71	64



**Figure 7: Comparative dissolution profile for poly ethylene oxide used formulations**

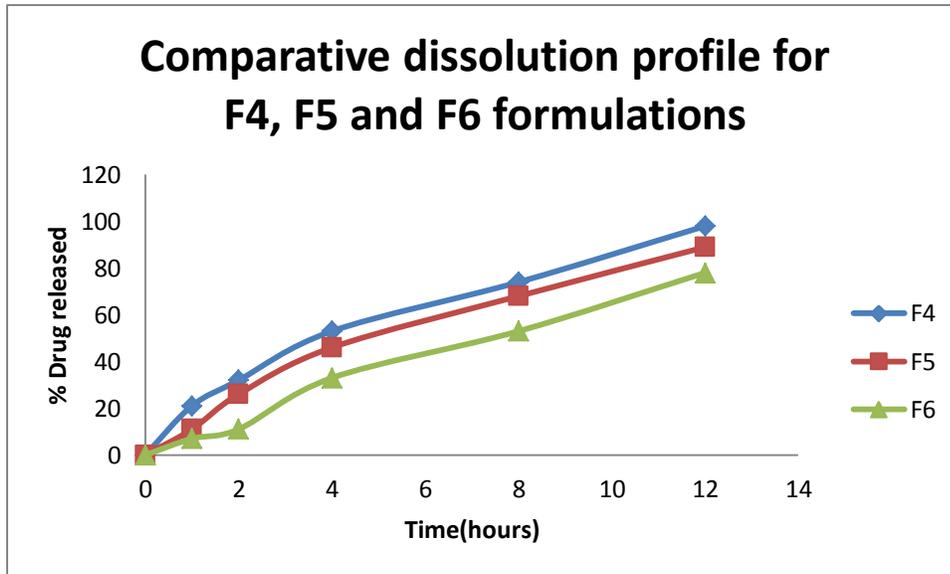


Figure 8: Comparative dissolution profile for HPMC K15M used formulations

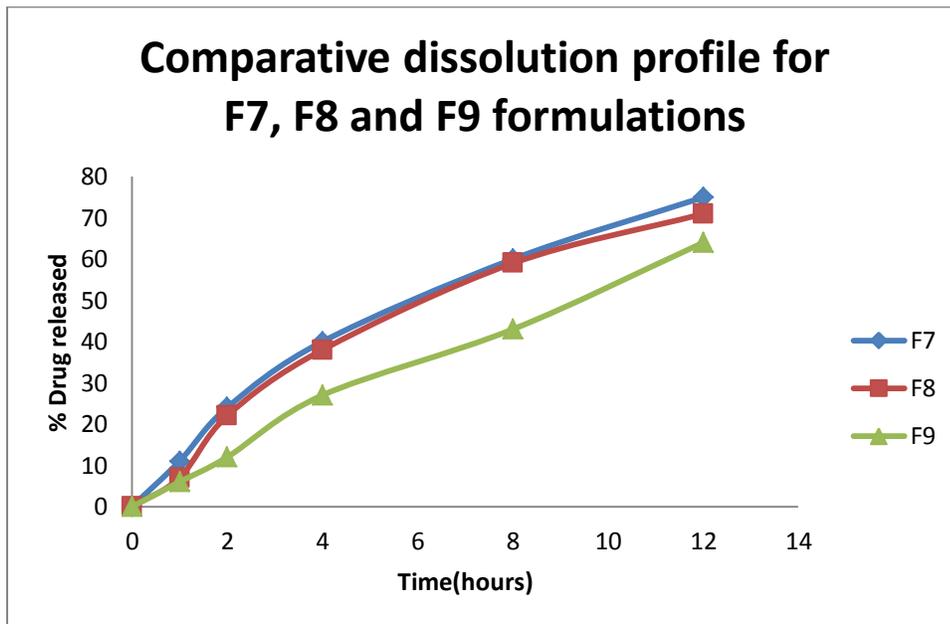
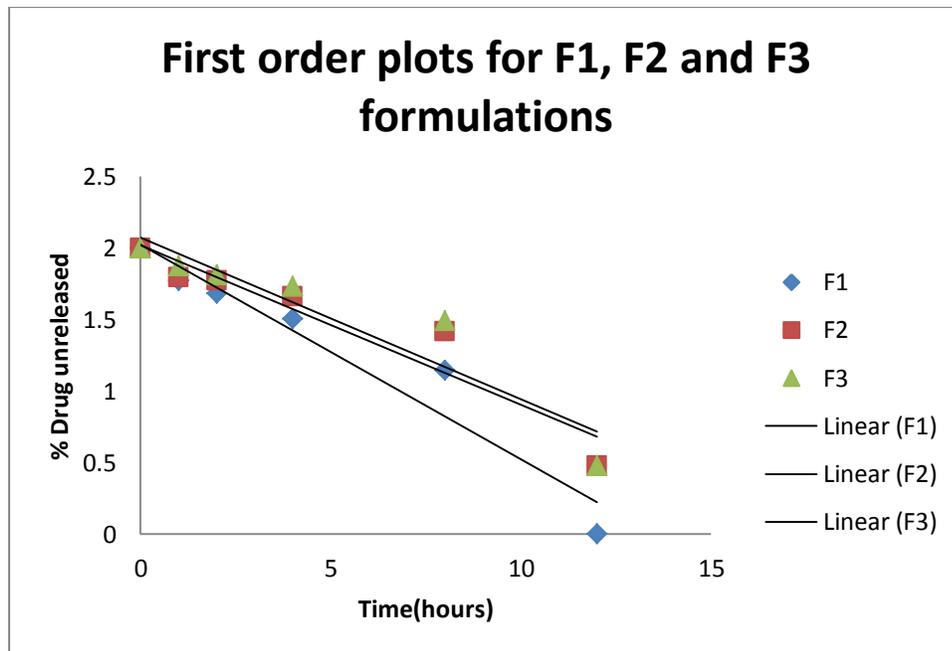


Figure 9: Comparative dissolution profile for Ethyl cellulose N50 used formulations



**Table 9: R<sup>2</sup> value and n result table**

Formulation code	R <sup>2</sup> value				N value
	Zero order	First order	Higuchi	Peppas	
<b>F1</b>	0.805	0.933	0.974	0.999	0.356
<b>F2</b>	0.882	0.901	0.981	0.948	0.381
<b>F3</b>	0.952	0.880	0.983	0.985	0.528
<b>F4</b>	0.952	0.896	0.990	0.996	0.616
<b>F5</b>	0.963	0.979	0.973	0.973	0.815
<b>F6</b>	0.989	0.972	0.924	0.979	1.008
<b>F7</b>	0.953	0.998	0.980	0.977	0.754
<b>F8</b>	0.946	0.993	0.966	0.941	0.895
<b>F9</b>	0.992	0.987	0.937	0.992	0.948



**Figure 10: First order plot for poly ethylene oxide used formulations**

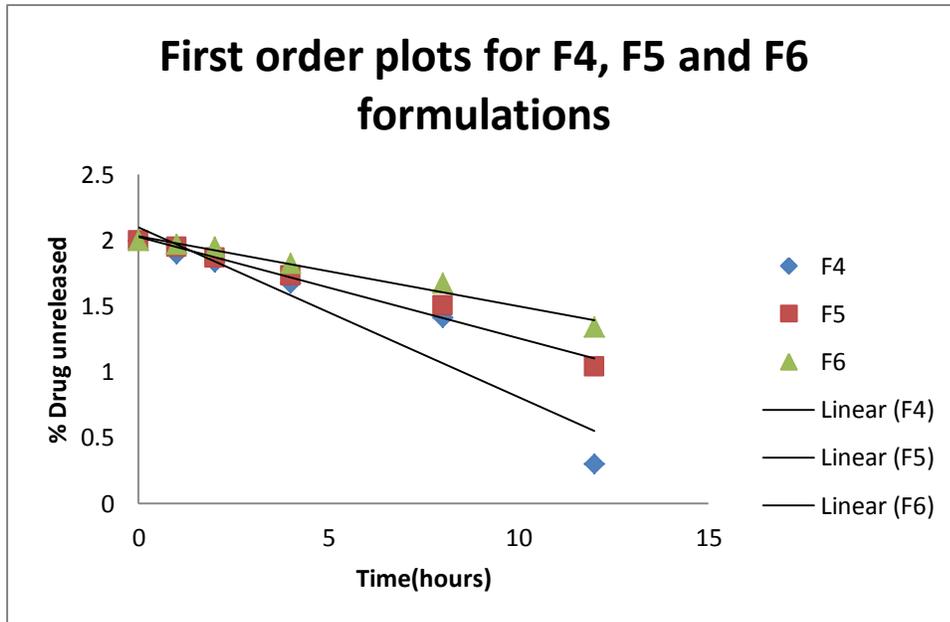


Figure 11: First order plot for HPMC K15M used formulations

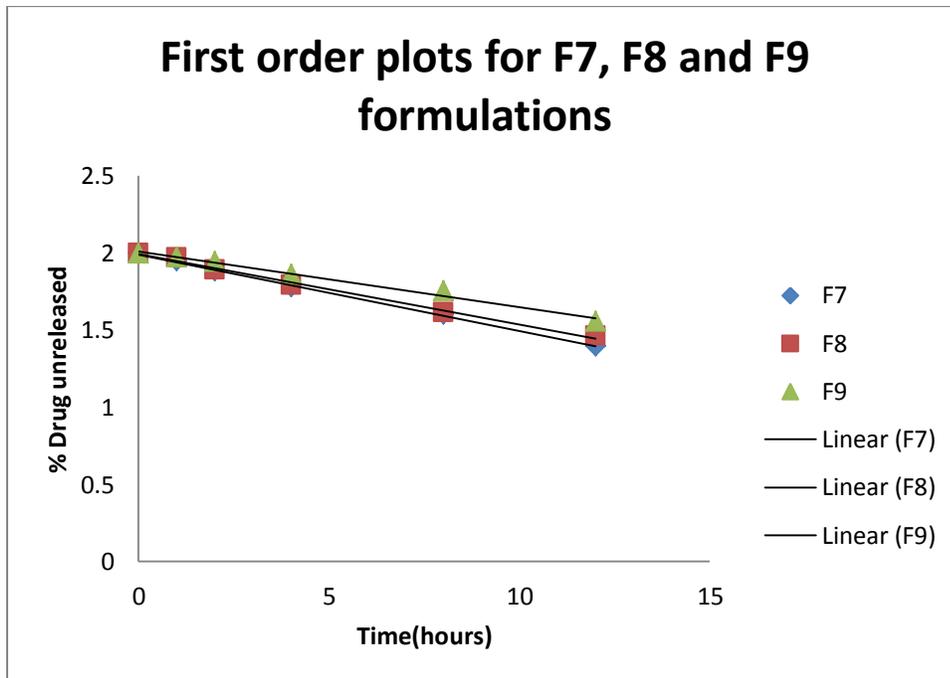


Figure 12: First order plot for Ethyl cellulose N50 used formulations

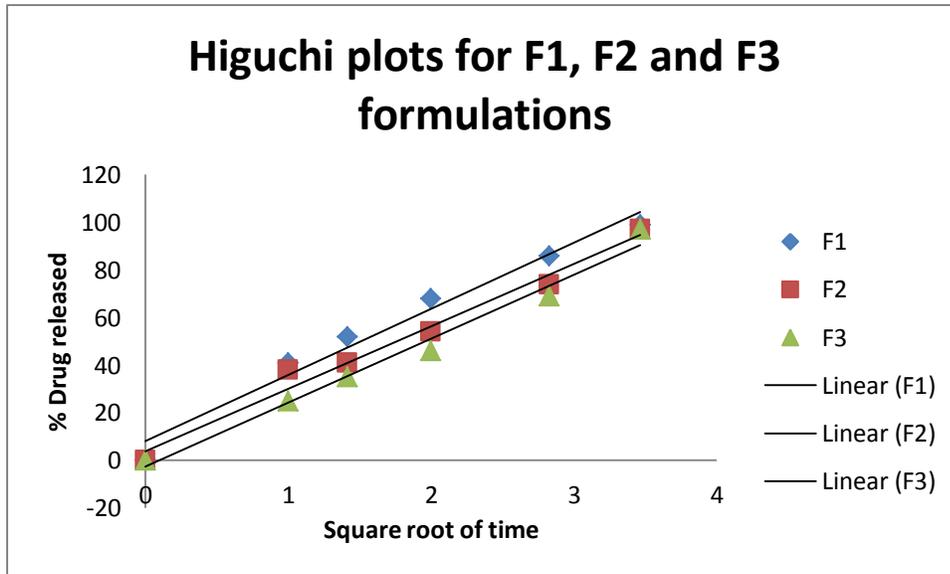


Figure 13: Higuchi plot for polyethylene oxide used formulations

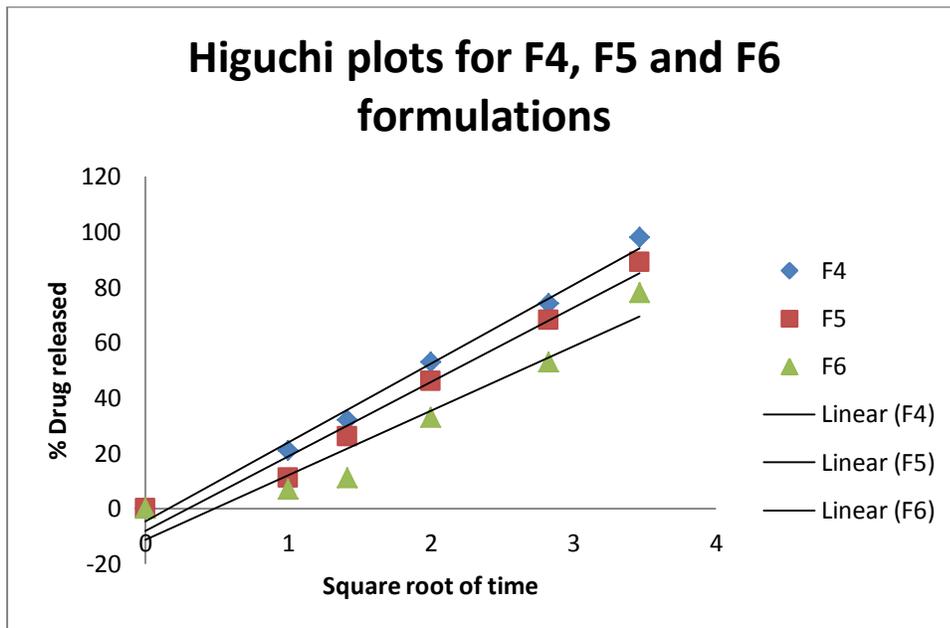


Figure 14: Higuchi plot for HPMC K15M used formulations

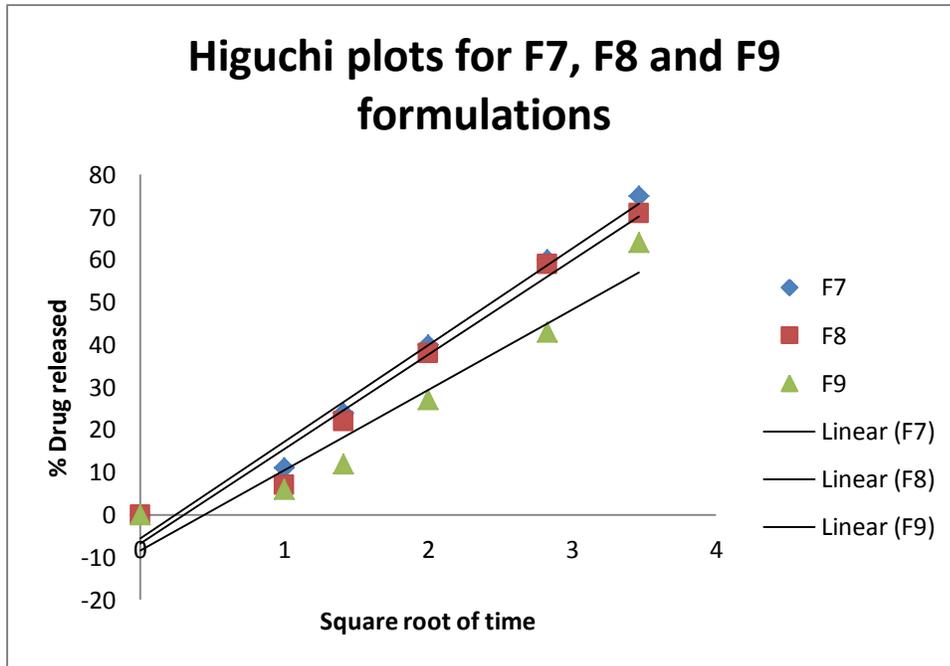


Figure 15: Higuchi plot for Ethyl cellulose N50 used formulations

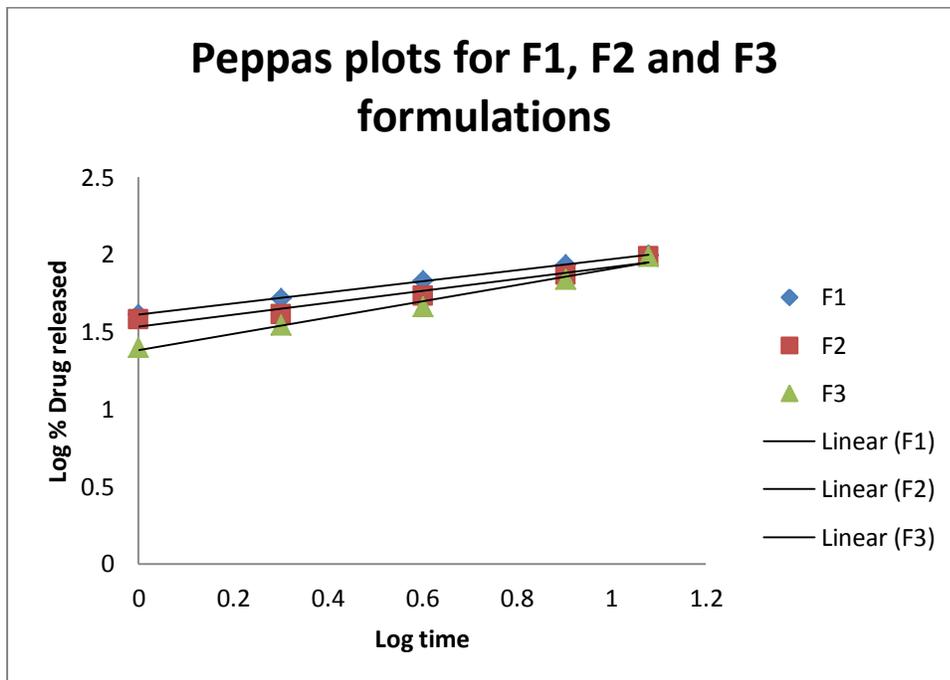


Figure 16: Korsmayerspepas plot for poly ethylene oxide used formulations

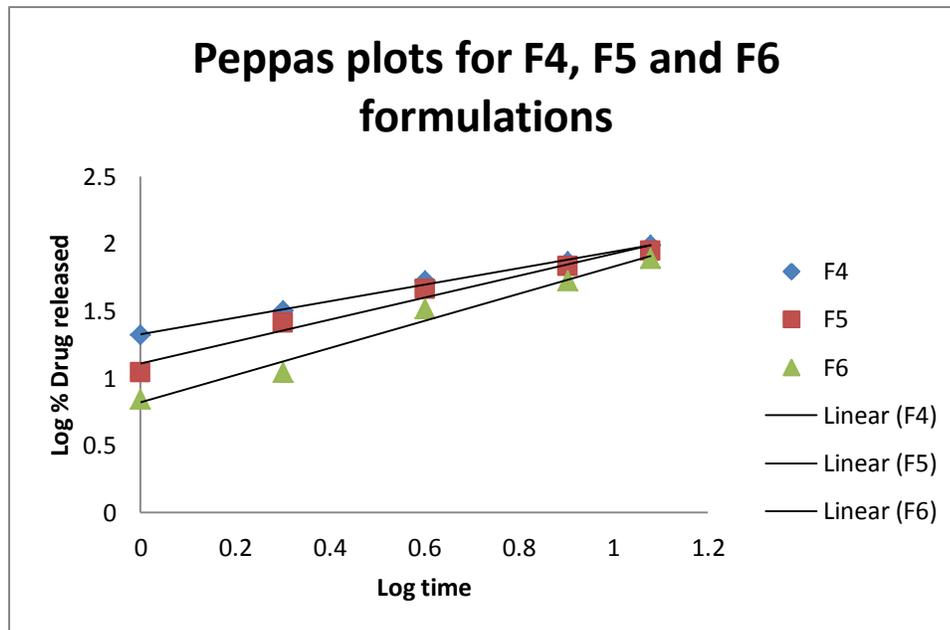


Figure 17: Korsmayerspepas plot for HPMC K15M used formulations

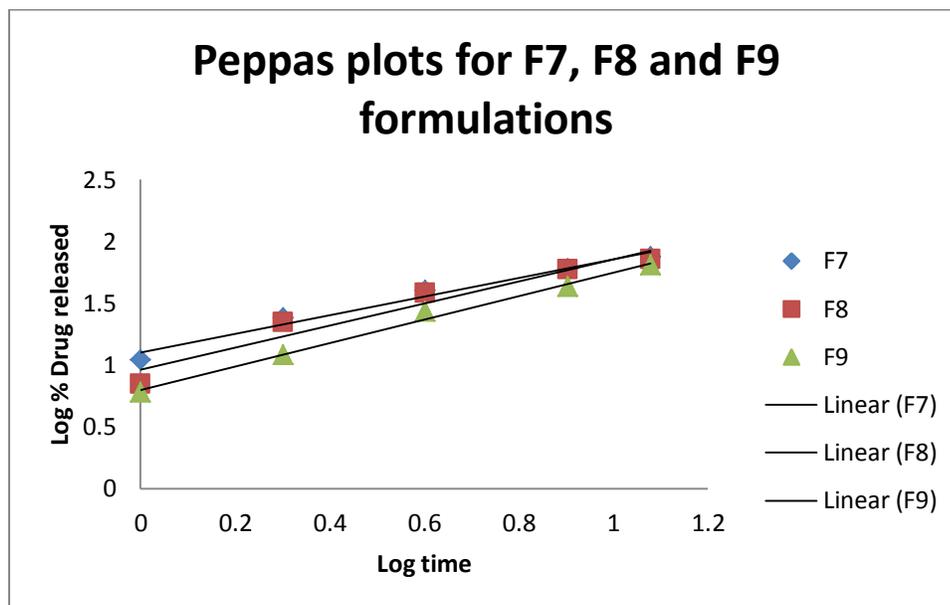


Figure 18: Korsmayerspepas plot for Ethyl cellulose N50 used formulations

#### Inference

- Among the different control release polymers Poly ethylene oxide, HPMC K15M and Ethyl cellulose were showing highest drug release retarding capacity
- F4 were showing the satisfactory results.
- For the F4 formulation diffusion exponent  $n$  value is in between 0.45 to 0.89 so they are following non fickian anomalous diffusion model



## Acknowledgment

The author takes this opportunity to thank the fellow co-authors for their assistance and contribution throughout the research work. Deserving a special mention to Chandrashekhar sir and Venkat Reddy sir from Pharma Train who have provided us with the chemicals as a gift and guided us, without whom this work would not have been possible.

## Summary and Conclusion

The approach of the present study was to make a comparative evaluation among these polymers (Poly ethylene oxide, HPMC K15M and Ethyl cellulose) and to assess the effect of physico-chemical nature of the active ingredients on the drug release profile.

The angle of repose, bulk density, tapped density and compressibility index results shown that the formulation is suitable for direct compression method.

These dosage forms have the ability to reduce the dosing frequency.

By increasing the polymer, the release rate of the drug decreases. F4 gave better release when compared to all formulations.

By the results we can confirm that the order of drug release is zero order.

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