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Journal of Pharmaceutics and Pharmacology Research
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Research Article

DESIGN, DEVELOPMENT AND CHARACTERIZATIONS OF ACYCLOVIR OSMOTIC TABLETS

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Received date: September 10,2018;**Accepted date : October 06,2018**; **Published date: October 08,2018.**
Citation for this Article: **Prasad Garepally**. Design, Development And Characterizations Of Acyclovir Osmotic Tablets. J. Pharmaceutics and Pharmacology Research , **Doi: http://dx.doi.org/ 10.31579/jppr.2018/005**

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Introduction

Oral drug delivery is the most widely utilized route of administration, among all the routes of administration. That has been explored for the systemic delivery drug through different pharmaceutical dosage forms. It can be said that at least 90%of all drugs used to produce systemic effect is by oral route.

Conventional oral drug delivery systems are known to provide an immediate release of drug, in which one 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. so overcome this limitation of oral route is replied by parenteral route. This route offers the advantage of reduced dose, targeting of site and avoiding GI stability, hepatic by-pass of drug molecule. (Leon, L., et al., 1986)

In the recent years, pharmaceutical research has led to the development of several novel drug delivery systems. The role of drug development is to take a therapeutically effective molecule with sub-optimal physicochemical and/or physiological properties and develop an optimized product that will still be therapeutically effective but with additional benefits such as:

- Sustained and consistent blood levels within the therapeutic window
- Enhanced bioavailability
- Reduced interpatient variability
- Customized delivery profiles
- Decreased dosing frequency
- Improved patient compliance
- Reduced side effects.

Based on the mechanism of the drug release can be classified as:

- Diffusion controlled (matrix and reservoir type of systems)
- Dissolution controlled (surface eroding, surface swelling type of systems)
- Osmotic drug delivery
- Multi particulate systems
- Enteric coated (pH dependent systems)

The most of novel drug delivery systems are prepared using matrix, reservoir or osmotic principle. In matrix systems, the drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the surrounding medium.

In contrast, reservoir systems have a drug core surrounded by a rate controlling membrane. The osmotic systems utilize the principles of osmotic pressure for the delivery of drugs in both the routes oral as well as Parenteral.

Controlled release (CR) technology has rapidly emerged over the past few decades as a new field offering approaches to the delivery of drugs into systemic circulation at predetermined rate. CR formulations can achieve optional therapeutic responses, prolonged efficacy as well as decrease toxicity duo to achieving predictable and reproducibility release rate of drugs for extended period of time.

Among all the routes of administration that have been explored for the development of controlled release (CR) systems, the reasons the oral route has attained the apex, because of obvious reasons. The reasons that the oral route achieved such popularity may be in fact attributed to its ease of administration as well as the traditional belief that by oral route of administration the drug is well absorbed as the food stuffs that are ingested regularly.

CR delivery systems provide desired concentration of drug at the absorption site permitting maintenance of plasma concentration within the therapeutic range and reducing dosing frequency. CR products provide significant benefits over immediate release formulations including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to a simplified dosing schedule.

In recent years, much attention has focused on novel drug delivery systems (NDDS). This is mainly due to low developmental cost and time required for creating a NDDS is also low. In contrast to conventional drug delivery systems, these systems will have number of advantages like increasing the market value, competitiveness and patients compliance.

There are many Novel drug delivery systems are in the market, per oral controlled release (CR) systems hold the major part in market share due to its obvious advantages like ease of administration and better patient compliance.(Verma., et al., 2001).

There are many designing options available to control or modify the drug release from a dosage form. Numerous technologies have been used to control the systemic delivery of drugs. One of the most interesting one is that employs osmotic pressure as an energy source for release of drugs.

Theoretical Aspects

Principles of osmosis

The first report of an osmotic effect dates to Abbe Nollet (1748), but pfeffer obtained the first quantitative measurements in 1877. In Pfeffer's experiment, a membrane permeable to water but impermeable to sugar was used to separate a sugar solution from pure water.

A flow of water then takes place into the sugar solution that cannot be halted until a pressure π is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure π of the sugar solution, is directly proportional to the solution concentration and the absolute temperature.

The phenomenon of confining a solution to a membrane, permeable only to the solvent molecules, is known as osmosis and the membrane that allows only the solvent molecules to pass throught it is known as semipermeable membrane (SPM). Therefore osmosis can be defined as the passage of solvent molecules into a solution (containing both solute and solvent molecules) thought SPM or passage of solvent molecules usually water takes place from the SPM from a region of lower concentration to higher concentration. This principle equalizes the escaping tendency of the solvent molecules, which is due to the difference in chemical potential across the SPM. It should be evident that osmosis can also take place when a concentrated solution is separated from a less concentrated solution by a semipermeable membrane. Thus passage of solvent (water) molecules continues until the osmosis pressure of the system i.e., inside and outside compartment becomes equal.

The principle of osmosis can be better understood by the application of the Van't Hoff equation, which suggests proportionality between osmosis pressure, concentration and temperature. According to Van't Hoff's equation, the osmosis pressure of a dilute solution will be equal to the pressure that solute would exert if it were a gas, occupying the same volume.

$$\pi V = nRT \quad (1)$$

Where π stands for osmosis pressure in atm, V stands for volume of solution in liters, n stands for the number of moles of solute, R stands for gas constant(0.082 liter atm/mole deg), and T stands for absolute temperature.

$$\pi = nRT/V \quad (2)$$

Osmosis pressure, like vapour pressure and boiling point is a colligative property of solution in which a non-volatile solute is dissolute in a volatile solvent.

Osmosis pressure can be defined as the pressure exerted as a result of osmosis or the pressure with which the solvent molecules cross from the semipermeable membrane or the required to stop the flow of solvent molecules from crossing the SPM is known as osmosis pressure.

The flow of solvent depends on SPM characteristics and different osmosis pressures between two sides of regions.

Osmosis pressure for concentrated solution of soluble solutes commonly used in controlled release formulation are extremely high, ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture (US patent number 4077407). These osmosis pressures can produce high water flows across semipermeable membrane. The osmotic water influx into osmosis pump across the SPM is given by the equation.

$$dv/dt = A/h \; Lp(\sigma\Delta\pi - \Delta\rho) C \quad (3)$$

where dv/dt is water influx, A and h are the membrane area and membrane thickness, respectively, Lρ is mechanical permeability, σ is the reflection coefficient and Δπ and Δρ are the osmosis and hydrostatic pressure difference respectively, between the inside and outside of the system, C is the concentration of compound in the dispensed fluid. As the size of the delivery orifice increases, hydrostatic pressure inside the system is minimized (Δπ > Δρ). Also, when the osmotic pressure of the formulation is large compared to the osmotic pressure of the environment, p can be substituted for Dp. Equation 1 then reduces to a much simpler expression in which constant K replaces the product Lp. After simplification, the following equation is obtained:

$$dM/dt = (A/h)Kp \times C \quad (4)$$

The release rate defined by Eq. 4 remains zero order as long as the terms in the equation remain constant. The first three terms on the right-hand side of Eq. 4 can be maintained constant through proper selection and optimization of the SPM. Therefore, a constant release of drug from the device is maintained as long as excess solid agent is present inside the device to maintain both p and C in Eq. 4 at constant levels. (Santus, G., et al., 1995)

Historical aspects of osmotic pumps

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems. Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. (Rose.,Nelson, J.F., 1955)

In 1955, they developed an implantable pump, which consisted of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. The drug and water chambers are separated by rigid semipermeable 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 this water flow, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device.

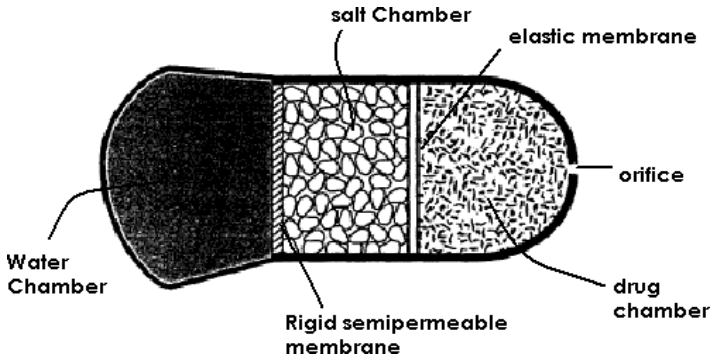


Fig 1: Schematic diagram of Rose and Nelson pump

Higuchi-Leeper pump

The design of Higuchi-Leeper pump represents the first simplified version of Rose-Nelson osmosis pump made by the Alza Corporation beginning in the early 1970s. An example of the one the pump is shown in Fig 2.

The Higuchi-Leeper pump has no water chamber, and device is activated by water imbibed from the surrounding environment. This means the pump can be prepared loaded with drug and then stored for weeks or months prior to use. The pump is activated when it is swallowed or implanted in the body. Higuchi- Leeper pumps contain a rigid housing and the semipermeable membrane is supported on a perforated frame. This type of pump usually has a salt chamber containing a fluid solution with excess solid salt.

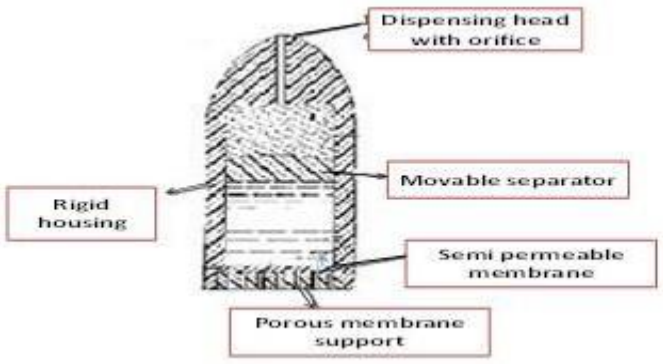


Fig 2: Schematic diagram of Higuchi-Leeper pump

Higuchi-Theeuwes Pump

In the early 1970s, Higuchi and Theeuwes developed another, even simpler variant of the Rose-Nelson pump. In the Higuchi-Theeuwes device, however, the rigid housing is dispensed with and the membrane acts as the outer casing of the dump. This membrane is quite sturdy and is strong enough to withstand the pumping pressure developed inside the device. The device is loaded with the desire drug prior to use. When the device is placed in an aqueous environment, release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing. Most of the Higuchi-Theeuwes pumps use a dispersion of solid in suitable carrier for the salt chamber of the device.

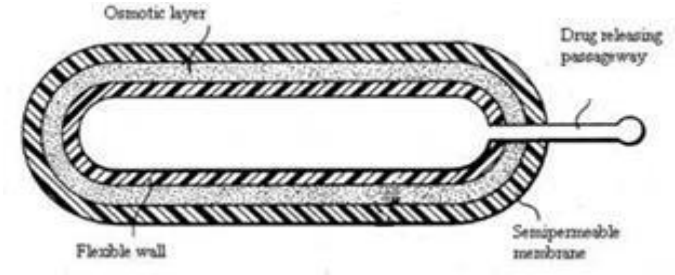


Fig 3: Schematic diagram of Higuchi-Theeuwes Pump

ORAL OSMOTIC PUMPS

Elementary osmotic pump

In 1975, the major leap in osmotic delivery occurred as the elementary osmotic pump for oral delivery of drugs was introduced. The pump consists of an osmotic core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. When this pump is exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and by the osmotic pressure of the core formulation. As the membrane is non-expandable, the increase in volume caused by the imbibition of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of saturated solution out of the device through the delivery orifice. This process continues at a constant rate until the entire solid agent inside the tablet has been dissolved and only a solution filled coating membrane is left. This residual dissolved agent continues to be delivered at a declining rate until the osmotic pressure inside and outside the tablet are equal. Normally, the Elementary osmotic pump delivers 60-80% of its contents at a constant rate, and there is a short lag time of 30-60 min as the system hydrates before zero order delivery from the Elementary osmotic pump is obtained. (Theeuwes, F., 1975).

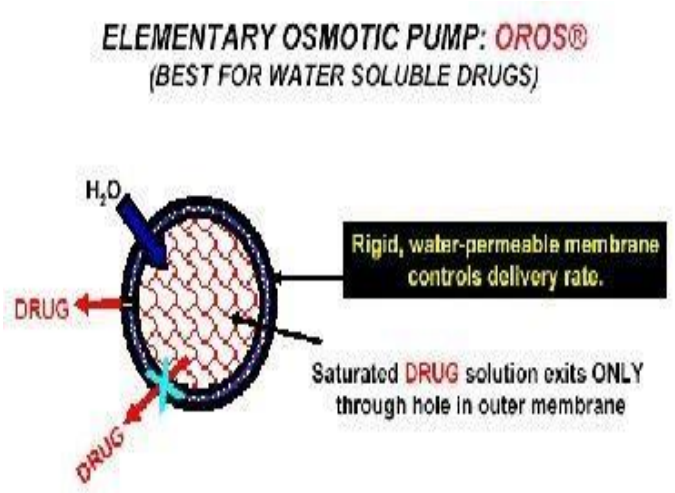


Fig 4: Schematic diagram of Elementary osmotic pump

Push pull Osmotic Pump

Push-pull osmotic pimp (PPOP) can be used for delivery of drugs having extremes of water solubility. As shown below fig 5. It is bilayer tablet coated with a SPM.

Drug along with osmagents is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents.The drug compartment is connected to the outside environment via a delivery orifice. After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug as fine dispersion via the orifice.

A number of modifications are available for this type of system such as delayed push-pull system (as used in covera HS, extended release for verapamil), multi-layer push-pull system (for pulsatile or delayed drug delivery), and push-stick system (for delivery of insoluble drugs requiring high loading, with an optional delayed, patterned or pulsatile release profile). (Wrong., et al., 1986).

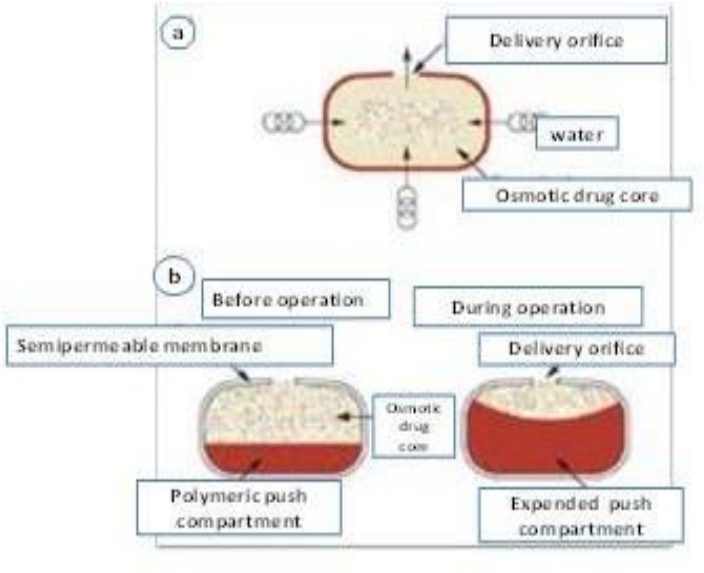


Fig 5: Schematic diagram of Push pull Osmotic Pump

Controlled porosity Osmotic Pumps (CPOP)

Controlled porosity osmotic pumps (CPOP) are similar to elementary osmotic pump, the only difference being that the delivery orifice from which the drug release takes place is formed by incorporation of a water-soluble additive in the coating. Once the tablet comes in contact with the aqueous media in the gastrointestinal tract (GIT), the water-soluble component dissolves and an osmotic pumping system results as shown below in Fig 6(Zentner, G.S., et al., 1985).

Nevertheless, the solubility of the agents to be delivered can be modulated, and these systems can be designed to deliver drugs having extremes of water solubility (Verma, R.K., et al., 1999).

The modification required depends mainly upon the dose intrinsic water solubility and osmotic pressure, and desired release rate of the drug.

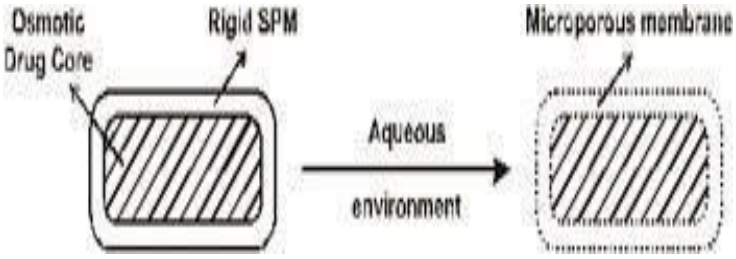


Fig 6: Schematic diagram of Controlled porosity Osmotic Pumps (CPOP)

OROS CT System

The OROS-CT TM system was designed for colon-targeted drug delivery. The system either comprises a single osmotic unit or it might contain as many as push-pull units enclosed within a hard gelatin capsule, immediately after ingestion the hard gelatin capsule shell dissolves.However, the push pull unit is prevented from absorbing water in the acidic environment of the stomach by the enteric coating. The osmotic pumping action results when the coating dissolves in the higher pH environment (pH>7) of the small intestine and the drug is delivered out of the orifice at a rate controlled by the rate of water transport across the membrane.

A class of osmotic pump is also designed to deliver liquid formulation. In the liquid OROSR or L-OROSR SOFTCAP TM, the liquid drug formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and the release rate – controlling membrane.

The L-OROSR HARDCAPTM is similar to the L-OROSR SOFTCAPTM comprising a drug suspension in a self-emulsifying formulation (SEF) to enhance the oral bioavailability of hydrophobic drugs. (Dong, L., et al., 2001)

Swellable core technology (SCT) is a new emerging field in osmotic drug delivery that can deliver drugs with moderate or poor aqueous solubility per and extended period of time. The SCT formulation consists of a core tablet that contains a drug composition and a water swellable composition. The drug composition contains the drug, an entraining polymer like polyethylene oxide, and osmotic agents. Whereas the swellable portion contains a non-ionic polymer (PEO) or and ionic polymer (croscamellose sodium or sodium starch glycolate) which swells and expands in volume after absorption of water. The drug composition may also contain solubilizers for example buffering agent which solubilize the drug by maintaining a pH environment that helps in drug dissolution and absorption. Furthermore, the drug and water swellable composition may contain other ingredients to improve the flow and compression characteristics of the blends, aiding in the preparation of tablets. In general, the components used in SCT formulation are safe commonly used in pharmaceutical products and available in pharmaceutical grades.

The drugs and water swellable composition in SCT formulation can be designed in various configurations. For example, they can be mixed together resulting in a uniform homogeneous core, or they can be physically separated from each other resulting in a layered configuration. The tablets cores are coated with a film coat of cellulose acetate of proper acetyl content and polyethylene glycol from an acetone – water solvent system. The film coating is them drilling either using a laser or a mechanical drill or slits are made to produce one or more exit ports for the release of drug.

The sandwich osmotic tablet system (SOTS) is composed of a sandwich osmotic tablet core (made of a middle push layer and two attached drug layers) surrounded by an SPM with two orifices on both side surface. After coming contact with the aqueous environment, the middle push layer containing swelling agents' swells and the drug is released from the delivery orifices. Because the system delivers from two opposite orifices, rather from the single orifices of the PPOP, it may decrease the potential local irritation of the drug (Liu, L., et al., 2000).

Asymmetric membrane capsules were developed in which the drug delivery device consists of a drug-containing core surrounded a membrane which has an asymmetric structure. i.e., it has a relatively thin, dense region supported on a thicker porous region. The capsule wall is made from a water insoluble polymer such as cellulose acetate. Unlike a conventional gelatin capsule the asymmetric membrane capsule does not dissolve immediately after ingestion. But it provides prolonged release of the active ingredient incorporated in the capsule.

(Cardinal, J.R., et al.,1997)

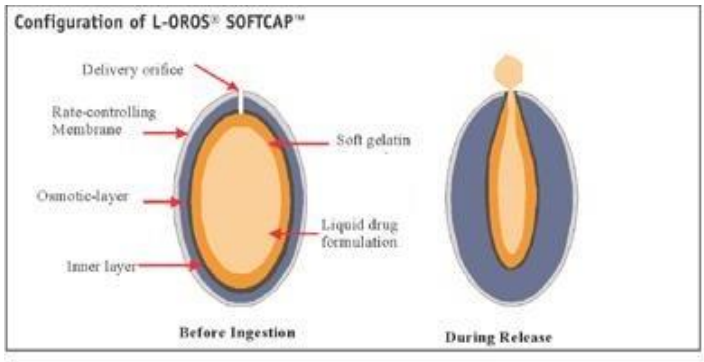


Fig 7: Schematic diagram of OROS CT System

Factors Affecting Drug Release Rate

Before discussing the formulation variables that affect the release of oral osmotic systems, it will be prudent to deal with some of the theoretical aspects. The delivery of agent from oral osmotic systems is controlled by the influx of solvent across the SPM, which in turn carries the agent to the outside environment. (Martin, A.,1993)

Solubility

It can be seen from Eq. 4 that the delivery rate of a drug from an osmotic pump depends to a large extent on the solubility of drug at saturation. Candidate drugs for osmotic delivery have water solubility in the range 50–300 mg/ml. 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 candidates for an OCODDS.

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.

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 excipients 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

Osmotic pressure is of a solution depending on number of discrete entities of solute presents in the solution. The release rate of a drug from a osmotic system is directly proportional to the osmotic pressure of the sore formulation in EOP design or in the drug reservoir of agent reservoir-osmotic engine- SPM design (e.g., AlzetR osmotic pump). For controlling drug release from these systems, it is important to optimize the osmotic pressure gradient between the inside compartment and the external environment.

It is possible to achieve maintain a constant osmotic pressure by maintaining solution of osmotic agent in the core compartment. If a drug does not possess sufficient osmotic pressure, an osmotically active agent can be added to the formulation.

Water-soluble salts of organic acids (sodium potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascrobate etc.), water-soluble amino acids (glycine, leucine, alanine, methionine) and organic polymeric osmogens (sodium carboxy methylcellulose, HPMC, hydroxyethy1, methy1 cellulose, cross-linked PVP, polyethylene oxide (PEO), carbopols, polyacry1 amides) can be used as osmogens. (Srinath, P., et al., 1998)

Category	Compound or Mixture	Osmotic pressure (atm)
Water-soluble salt of inorganic acids	Potassium chloride	245
	Potassium sulfate	39
	Potassium hydrogen phosphate	105
	Sodium hydrogen phosphate	28
	Sodium chloride	356
Carbohydrates	Mannitol	38
	Sucrose	150
	Lactose-fructose	500
	Dextrose-fructose	450
	Sucrose-fructose	430
	Fructose	23
	Lactose	82
	Dextrose	415
	Mannitol-fructose	130
	Mannitol-lactose	170
	Mannitol-sucrose	225
	Mannitol-dextrose	225
	Lactose-dextrose	225
Inorganic sodium salts	Sodium phosphate tribasic, 12 H_2o	36
	Sodium phosphate dibasic $7H_2o$	31
	Sodium phosphate monobasic, H_2o	28
	Sodium phosphate dibasic, $12H_2o$	31
	Sodium phosphate dibasic anhydrous	29
Other miscellaneous substances	Citric acid	69
	Trataric acid	67
	Fumaric acid	10
	Adipic acid	8
	Sorbitol	84
	Xylitol	104
	Maleic acid	117

Table 1: **List Of Compound That Can Be Used As Osmogens**

Osmotic System Pressures are Laser Drilling

Laser drilling is one of the most commonly used techniques to create deliver orifice in the osmotic tablets. In simple words, the tablets in which holes are to be formed are changed in the hopper. The tablets drop by gravity into the slots of the rotation feed wheel are carried at a predetermined velocity to the passageway forming station. The walls of the tablets absorb the energy of the beam and gets heated ultimately causing piercing of the wall and, thus forming passageway. After completion, the tracking mirror oscillation counterclockwise back to its starting position to track the next tablet. It is possible to control the size of the passageway by varying the laser power, firming duration (pulse time), thickness of the wall, and the dimension of the beam at the wall.

Systems with passageway formed in situ

Oral osmotic systems in which delivery passageway is formed in situ are described in US patent No. 5,736,159 (Chen et al,. 1982)

The system described consists of a tablet core of the drug along with the water swellable polymers and osmotic agents, which surrounded by a rate-controlled membrane.

In contact with the aqueous environment, water is imbibed osmotically at a controlled rate and water swellable polymer expands as the osmotic agents dissolves and increases the osmotic pressure inside the tablets. This results in a rate-controlled slight expansion of the partially hydrates core. The expansion of core cause a small opening to form at the edge of the tablets (weakest point in the membrane) from where the contents of the formulation are released. In the working examples, core tablets of nifedipine were prepared using polyethylene oxide as a water swellable agent and coated with a rate controlling membrane. The osmotic systems were able to maintain plasma concentration of the drug within the therapeutic range for 24 hrs.

Use of modified punches

Use of modified punches for producing a delivery orifice in osmotic dosage forms has also been described in the literature.

The dosage form is pierced using a piercing and unsheathed upon application of compression force. The coating powder top be compressed in charged to the die mold and unpierced tablet core is placed upon it. Additional quotation of coating powder is added to the die mod, subsequent to which both compression and piercing are done simultaneously. (A.D.Ayer et al., 1991)

Use of pore formers

CPOP are extension of EOPs and are essentially similar, expect that there is no need to create a delivery orifice, drug release from these types of system takes place through controlled porosity pores formed in situ. In corporation of water-soluble additive in the membrane wall is the most widely reported method for the formation of pores in CPOP (G.M Zentner et al., 1990; J.L.Haslam et al., 1989).

These water soluble additives dissolve on coming in contact with water, leaving behind pores in the membrane through which drug release takes place. Drug release from these types of system is independent of pH and has been shown to follow zero-order kinetics (Zentner et al., 1985).

These erodible or leachable materials produce one or more passageways with difference geometrical shapes. The pores may also be formed in the wall prior to the operation of the systems by has formation within curing polymer solution, resulting in voids and pores in the final form of the membrane. The pores may also be formed in the walls by the volatilization of components in the polymer solution or by chemical reaction in the polymer solution leading to evaluation of gases prior to application or drugging application of the solution to the core tablets resulting in the creation of the polymer foams serving as the porous wall from where the drug release can take place (Zentner et al., 1990).

Membrane type and characteristics

The choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. Recalling Eq.4, which describes the volume flow, one can easily recognize the importance of the SPM in controlling release of the drug. The membrane must possess certain performance criteria (Theeuwes.F., 1975).

Type and nature of polymer

Since the membrane in osmotic systems is semipermeable in nature, any polymer that is permeable to water but impermeable to solute can be selected. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diaceate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, etc. Cellulose ethers like ethyl cellulose and eudragits.

Polymer membrane	*Water vapour transmission rates*
Polyvinyl alcohol	*100*
Polyurethene	*30-150*
Ethylcellulose	*75*
Methylcellulose	*70*
Cellulose acetate	*40-75*
Cellulose acetate butyrate	*50*
Polyvinylchloride(cast)	*10-20*
Polyvinylchloride(extruded)	*6-15*
Polycarbonate	*8*
Ethylene vinyl acetate	*1-3*
Poly vinyl chloride	*1*
Polypropylene	*0.7*

Table 2: List of semipermeable polymers with their water

Ethyl cellulose is also widely used in the formulation of membranes for oral osmotic systems. However, the water permeability of pure ethyl cellulose membrane is very low that may result in slow release in slow release of the drugs. Nevertheless, drug release from osmotic systems coated with ethyl cellulose membrane can be enhance by the incorporation of water-soluble additives addition of HPMC in the coating composition improves the permeability of ethyl cellulose membranes.

Tablets core of potassium chloride coated with a mixture of ethyl cellulose and up to 24% of HPMC were shown to release the contents mainly through osmotic mechanism. (B. Lindstedt et al., 1989)

Effect of type of plasticizer on release profile

Plasticizers can change viscoelastic behavior of polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films. The effect of different types of plasticizers (TA and polyethylene glycols) on the water permeation and mechanical properties were studied. The water permeability of CA films was found to decrease with increasing plasticizer concentration to a minimum and then increases with higher concentration of plasticizer.(J. Guo.1993)

Membrane Thickness

Thickness of the membrane has a profound effect on the drug release from osmotic systems. It can be seen Eq. 4, that release rate from osmotic systems is inversely proportional to membrane thickness. Pellets of phenylpropanolamine coated with aqueous ethyl cellulose based films were found to release drugs mainly through the mechanism of osmotic pumping and diffusion. (Ozturk,A.G. et al., 1990).

On studying the release as function of coating thickness, it was found that as the coating thickness increased from 9 to 50 µm, the drug release decreased in an inversely proportional manner. In case of monolithic osmotic tablets of nifedipine, release rates were found to decrease with increase in membrane thickness from 85 to 340µm (L. Liu et al., 2000).

An increased resistance of the membrane to water diffusion resulted in this effect.

On the other hand, thickness of the membrane in case of asymmetric coating was found to have insignificant effect on drug release. Release rates were found to be virtually unaffected by the overall membrane thickness in the range of 95-150 µm. (Herbig S.M. et al., 1995).

Evaluation of Osmotically controlled drug delivery systems

Over the past few years there is increase in the development and commercialization of controlled-release dosage forms has necessitated changes in evaluation aspects of them. This is to provide in-house quality control tests and to furnish regulatory agencies with the experimental evidence that the dosage forms delivers the drug in a controlled and reproducible manner. There is a need for establishing in-vitro-in-vivo correlations to simulate the drug evaluation in the in-vivo system. [Hanlon J C et al., 2008].

Advantages

A part from the general advantages shared by conventional CR systems. OCODDSs have several other unique advantages. Osmotic delivery is a versatile technology that can be used as a powerful research tool to determine various pharmacokinetic parameters and pharmacodynamic response of drugs in animals and humans.

1. Delivery of drug from osmotic pumps can be designed to follow true Zero-order Kinetics. Constant delivery rate is an important specification for chronic treatment. In addition, based upon the requirements, drug delivery can be modulated to achieve pulsatile or delayed zero-order delivery.
2. Drug release from osmotic pumps is minimally affected by the gastric pH and hydrodynamic condition of the body. This is mainly because of the special properties of this semi-permeable membrane employed in the coating of osmotic formulations. The delivery rate is independent of the variation in pH throughout the GIT and GI motility.
3. Higher release rates can be obtained from osmotic systems than with conventional diffusion based drug delivery systems.
4. The delivery of drug takes place in solution form, which is ready for absorption. Thus it is an in situ prepared liquid dosage form.

5. It is possible design an osmotic pump for drug with wide range of water solubility.
6. The delivery rate of drug(s) from these systems is highly predicable and programmable. The in vitro rate can be accurately predicated since the system well described by the equation.
7. A high degree of in vitro/in-vivo correlation can be obtained from osmotic pumps. The Significant in vitro and in vivo correlation for a verapamil oral osmotic system was studied. (Gupta et al. 1996)
8. Drug release from the osmotic systems is minimally affected by the presence of food.

EXCIPIENT PROFILE

CELLULOSE ACETATE

1. Nonproprietary Names

- BP: Cellulose acetate
- PhEur: Cellulosi acetas
- USPNF: Cellulose acetate

2. Synonyms

- Acetyl cellulose; cellulose diacetate; cellulose triacetate.

3. Chemical Name

- Cellulose acetate
- Cellulose diacetate
- Cellulose triacetate

4. Applications

- Cellulose acetate is used as a semipermeable coating on tablets, especially on osmotic pump type tablets and implants. This allows for controlled, extended release of actives.
- Cellulose acetate films, in conjunction with other materials, also offer sustained release without the necessity of drilling a hole in the coating as is typical with osmotic pump systems.
- Cellulose acetate and other cellulose esters have also been used to form drug-loaded microparticles with controlled-release characteristics.
- Cellulose acetate films are used in transdermal drug delivery systems and also as film

coatings on tablets or granules for taste masking.

- Extended-release tablets can also be formulated with cellulose acetate as a directly compressible matrix former.10 The release profile can be modified by changing the ratio of active to cellulose acetate and by incorporation of plasticizer, but was shown to be insensitive to cellulose acetate molecular weight and particle size distribution.
- Therapeutically, cellulose acetate has been used to treat cerebral aneurysms, and also for spinal perimedullary arteriovenous fistulas.

5. Description

Cellulose acetate occurs as a white to off-white powder, free-flowing pellets, or flakes. It is tasteless and odorless, or may have a slight odor of acetic acid.

6. Stability and Storage Conditions

Cellulose acetate is stable if stored in a well-closed container in a cool, dry place. Cellulose acetate hydrolyzes slowly under prolonged adverse conditions such as high temperature and humidity, with a resultant increase in free acid content and odor of acetic acid.

7. Incompatibilities

Cellulose acetate is incompatible with strongly acidic or alkaline substances. Cellulose. acetate is compatible with the following plasticizers: diethyl phthalate, polyethylene glycol,triacetin, and triethyl citrate.(handbook of excipients).

POTASSIUM CHLORIDE

1. Applications in Pharmaceutical Formulation or Technology:

• Potassium chloride is widely used in a variety of parenteral and nonparenteral pharmaceutical formulations. Its primary use, in parenteral and ophthalmic preparations, is to produce isotonic solutions.

• Potassium chloride is also used therapeutically in the treatment of hypokalemia Many solid-dosage forms of potassium chloride exist including: tablets prepared by direct compression1–4 and granulation;5,6 effervescent tablets; coated, sustained-release tablets;7–10 sustained-release wax matrix tablets;11 microcapsules;12 pellets; and osmotic pump formulations.13,14

• Experimentally, potassium chloride is frequently used as a model drug in the development of new solid-dosage forms, particularly for sustained-release or modified-release products. Potassium chloride is also used widely in the food industry as a dietary supplement, pH control agent, stabilizer, thickener, and gelling agent. It can also be used in infant formulations.

2. Description

Potassium chloride occurs as odorless, colorless crystals or a white crystalline powder, with an unpleasant, saline taste. The crystal lattice is a face-centered cubic structure.

3. Solubility

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Practically insoluble
Ethanol (95%)	1 in 250
Ether	Practically insoluble
Glycerin	1 in 14
Water	1 in 2.8 1 in 1.8 at 100°C

Table 3: Solubility of KCl

4. Stability and Storage Conditions

Potassium chloride tablets become increasingly hard on storage at low humidities. However, tablets stored at 76% relative humidity showed no increase or only a slight increase in hardness and hardness on aging.2 Aqueous potassium chloride solutions may be sterilized by autoclaving or by filtration. Potassium chloride is stable and should be stored in a well-closed container in a cool, dry place. (Parikh, M.,)

5. Incompatibilities

Potassium chloride reacts violently with bromine trifluoride and with a mixture of sulfuric acid and potassium permanganate. The presence of hydrochloric acid, sodium chloride, and magnesium chloride decreases the solubility of potassium chloride in water. Aqueous solutions of potassium chloride form precipitates with lead and silver salts. Intravenous aqueous potassium chloride solutions are incompatible with protein hydrolysate.

6. Method of Manufacture

Potassium chloride occurs naturally as the mineral sylvite or sylvine; it also occurs in other minerals such as sylvinite, carnallite, and kainite. Commercially, potassium chloride is obtained by the solar evaporation of brine or by the mining of mineral deposits.

Mannitol

Functional Category

Confectionery base; coating agent; granulation aid; suspending agent; sweetening agent; tablet binder; tablet and capsule diluent; tablet filler; therapeutic agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology.

Sucrose is widely used in oral pharmaceutical formulations. Sucrose syrup, containing 50–67% w/w sucrose, is used in tableting as a binding agent for wet granulation. In the powdered form, sucrose serves as a dry binder (2–20% w/w) or as a bulking agent and sweetener in chewable tablets and lozenges.

That contain large amounts of sucrose may harden to give poor disintegration.

Sucrose syrups are used as tablet-coating agents at concentra-tions between 50% and 67% w/w. With higher concentrations, partial inversion of sucrose occurs, which makes sugar coating difficult. Sucrose syrups are also widely used as vehicles in oral liquid-dosage forms to enhance palatability or to increase viscosity. Sucrose has been used as a diluent in freeze-dried protein products. Sucrose is also widely used in foods and confectionery, and therapeutically in sugar pastes that are used to promote wound healing.

Sucrose

Description

Sucrose is a sugar obtained from sugar cane (Saccharum officinarum Linne ´ (Fam. Gramineae)), sugar beet (Beta vulgaris Linne ´ (Fam. Chenopodiaceae)), and other sources. It contains no added substances. Sucrose occurs as colorless crystals, as crystalline masses or blocks, or as a white crystalline powder; it is odorless and has a sweet taste.

Microcrystalline Cellulose

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluents	20–90
Tablet disintegrant	5–15
Tablet binder/diluents	20–90

Description

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Solubility

slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agent. (Owen S.et al.)

POVIDONE (PVP)

Applications in Pharmaceutical Formulation or Technology .

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. [Parikh, M.]

Uses

Use	Concentration (%)
Carrier for drugs	Carrier for drugs
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

Table 5: Uses of povidone in percentage concentration.

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidone with K-values equal to or lower than 30 are manufactured

by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidone are manufactured by drum drying and occur as plates.

MAGNESIUM STEARATE

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

TRIETHYL CITRATE

Functional Category: Plasticizer.

Applications in Pharmaceutical Formulation or Technology

Triethyl citrate and the related esters acetyltriethyl citrate, tributyl citrate, and acetyltributyl are used to plasticize polymers in formulated pharmaceutical coatings.

The coatingapplications include capsules, tablets, beads, and granules for taste masking , immediaterelease, sustained-release, and enteric formulations.

Triethyl citrate is also used as a direct food additive for flavoring, for solvency, and as a surface active agent.

Description

Triethyl citrate is a clear, odorless, practically colorless, oily liquid.

Solubility: soluble 1 in 125 of peanut oil, 1 in 15 of water. Miscible with ethanol (95%), acetone, and propan-2-ol.

Viscosity (dynamic): 35.2 mPa s (35.2 cP) at 25°C

Fructose

Functional Category

Dissolution enhancer; flavoring agent; sweetening agent; tablet diluent.

Applications in Pharmaceutical Formulation or Technology

Fructose is used in tablets, syrups, and solutions as a flavoring and sweetening agent. The sweetness-response profile of fructose is perceived in the mouth more rapidly than that of sucrose and dextrose,

Which may account for the ability of fructose to enhance syrup or tablet fruit flavors andmask certain unpleasant vitamin ormineral 'off-flavors'. The increased solubility of fructose in comparison to sucrose is advantageous in syrup or solution formulations that must be refrigerated, since settling or crystallization of ingredients is retarded. Similarly, the greater solubility and hygroscopicity of fructose over sucrose and dextrose helps to avoid 'cap-locking' (sugar crystallization around the bottle cap) in elixir preparations. Fructose also has greater solubility in ethanol (95%) and is therefore used to sweeten alcoholic formulations. The water activity of a sweetener influences product microbial stability and freshness. Fructose has a lower water activity and a higher osmotic pressure than sucrose. Syrup formulations may be made at lower dry-substance levels than sugar syrups without compromising shelf-life stability. It may be necessary to include a thickener or gelling agent to match the texture or viscosity of the sugar-equivalent formulation. Fructose is sweeter than the sugar alcohols mannitol and sorbitol, which are commonly used as tableting excipients. Although fructose is effective at masking unpleasant flavors in tablet formulations, tablets of satisfactory hardness and friability can only be produced by direct compression if tablet presses are operated at relatively slow speeds. However, by the combination of crystalline fructose with tablet-grade sorbitol in a 3 : 1 ratio, satisfactory direct-compression characteristics can be achieved. A directly compressible grade of fructose, containing a small amount of starch (Advantose FS 95, SPI Pharma) is also commercially available. Pregranulation of fructose with 3.5% povidone also produces a satisfactory tablet excipient.

The added sweetness of fructose may also be used to advantage by coating the surface of chewable tablets, lozenges, or medicinal gums with powdered fructose. The coprecipitation of fructose with hydrophobic drugs such as digoxin has been shown to enhance the dissolution carrier upon coprecipitation, thereby allowing hydrophobic drugs to be more readily wetted.

Description

Fructose occurs as odorless, colorless crystals or a white crystalline powder with a very sweet taste.

profile of such drugs. Fructose apparently acts as a water-soluble

Materials And Methods

Table 6 : List of Materials used in the present work are as follows.

S NO	Materials	Name of the supplier
1	Acyclovir**(mg)**	Chandra labs, hyd
2	Potassium chloride	MYL CHEM Mumbai
3	Sodium chloride	MYL CHEM Mumbai
4	Mannitol	MYL CHEM Mumbai
5	Sucrose	MYL CHEM Mumbai
6	Fructose	S.D Fine chem. LTD Mumbai
7	PVP K-30	S.D Fine chem. LTD Mumbai
8	MCC	MYL CHEM Mumbai
9	Magnesium Stearate	MYL CHEM Mumbai
10	Cellulose acetate	S.D Fine chem. LTD Mumbai

Table 7: List of Equipments used in the present work are as follows

S.No	Instruments	Source
1	Electronic balance	Shimadzu
2	UV/Visible Spectrophotometer	Corporation-BL-220H
3	FTIR spectrophotometer	Corporation japan
4	Magnetic stirrer	Remi motor equipments
5	Dissolution apparatus	Shimadzu
6	Oven	Biotech india.
7	pH meter	Shital scientific industries
8	Compression machine	Cadmach machinery

METHODOLOGY

Preformulation Studies

Construction of Standard Graph of Acyclovir in 0.1N Hcl
Preparation of 0.1N Hcl
Take 8.5ml of Hcl in distilled water and make up to 1000ml with distilled Water to get 0.1N Hcl
Construction of Standard Graph of Acyclovir in 0.1N Hcl

Preparation of stock solution

Accurately weighed amount of 25 mg was transferred into a 25ml volumetric flask. And the volume was made up to 25 mL with 0.1N Hcl. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'.

Preparation of working standard solution

From this stock solution 10ml was taken and diluted to 100 mL with 0.1N Hcl which has given the solution having the concentration of 100 mcg/mL.

Drug – Excipient Compatibility Study:

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation.1-2 mg of solid fine powder of drug and 200-300 mg of dry powder of KBr(IR grade) were taken in a mortar and mixed well with the help of a spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400cm-1 by FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

FORMULATION OF OSMOTIC TABLET

- Osmotic tablets of were prepared by direct compression method.
- Manufacturing Procedure:
- Micro crystalline cellulose, osmotic agents, PVP K30 were weighed according to the given table and sifted through 40 mesh.
- To the above blend acyclovir was added and sifted through 18 mesh.
- The sifted materials were mixed for 10min.

Table 8: Various formulations of ODDS were made as given table .

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8
Acyclovir(mg)	200	200	200	200	200	200	200	200
Potassium chloride	0.5	-	-	-	-	-	-	-
Sodium chloride	-	0.5	-	-	-	0.75	1.0	1.25
Mannitol	-	-	0.5	-	-	-	-	-
Sucrose	-	-	-	0.5	-	-	-	-
Fructose	-	-	-	-	0.5	-	-	-
PVP K-30	5	5	5	5	5	5	5	5
MCC	qs	qs	qs	qs	qs	qs	qs	qs
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total wt	400	400	400	400	400	400	400	400

Coating with semi-permeable polymer

Core tablets were coated by using a coating machine with a perforated pan. A solution of cellulose acetate in acetone at a concentration of (4%w/v), containing TEC at concentration of 10% of w/w of cellulose acetate, level of plasticizer (TEC) was used as the coating solution. To the acetone, slowly cellulose acetate added with proper mixing. In between, plasticizer was added drop wise and through mixing was done to dissolve the cellulose acetate. Addition of plasticizer in the coating solution improves film properties like film flexibility. The final coating solution was filtered through # 80 sieve. The composition solution used is mentioned in table below.

Table 9 : Coating solution composition

INGREDIENTS	WEIGHT	CONCENTRATION (%)
Cellulose acetate	40gms	4%
Triethyl citrate	4 gms	0.4
Acetone	1000ml	Quantity sufficient

PREFORMULATION STUDY

Pre-compression parameters

a) Angle of repose.
b) Bulk density & Tapped density.
c) Hausner ratio.
d) Compressibility index (%)

Angle of repose	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Compressibility index	Flow property
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor
>40	Very very poor

Kinetic Analysis of Dissolution Data

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent , Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K0t \quad (1)$$

where, K0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC0-K1t/2.303 \quad (2)$$

where, C0 is the initial concentration of drug and K1 is first order constant.

$$Q = KHt1/2 \quad (3)$$

where, KH is the constant reflecting the design variables of the system.

$$Q01/3–Qt1/3= KHCt \quad (4)$$

where, Qt is the amount of drug remained in time t, Q0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model);

Log cumulative of % drug remaining vs. time (First order kinetic model);

Cumulative % drug release vs. square root of time (Higuchi model);

And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

Mechanism of drug release

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$Mt / M\infty = Ktn \quad (5)$$

where Mt / M∞ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table, for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

Table 12: Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

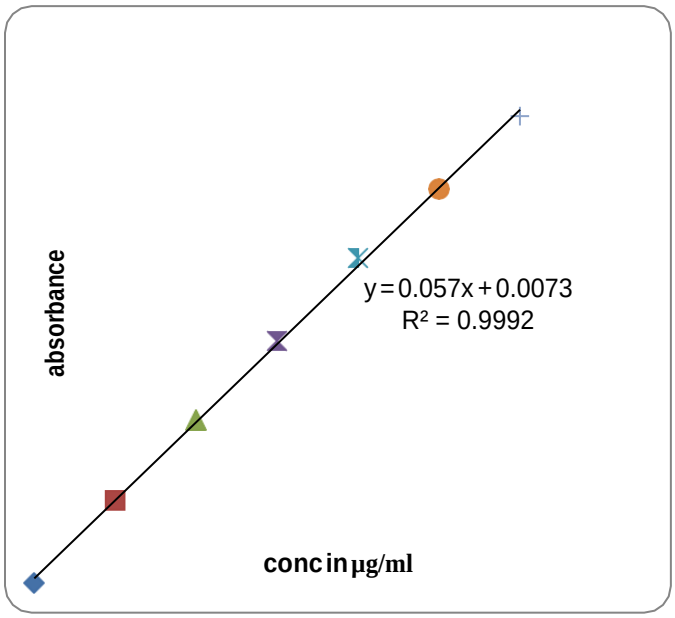
Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Results And Discussion

Preparation of standard calibration curve of Acyclovir:

Table 13 : Concentration and absorbances of Acyclovir in 0.1N Hcl

S.No	Concentration	Absorbance at 254nm
1	0	0
2	2	0.121
3	4	0.238
4	6	0.354
5	8	0.475
6	10	0.576
7	12	0.682

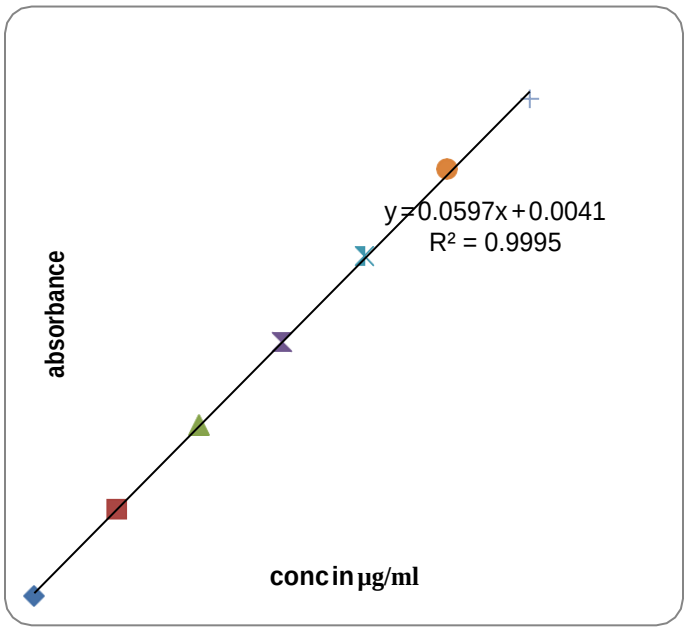


Graph 1 - calibration curve of Acyclovir

Standard Graph of Acyclovir in 6.8pH phosphate buffer:

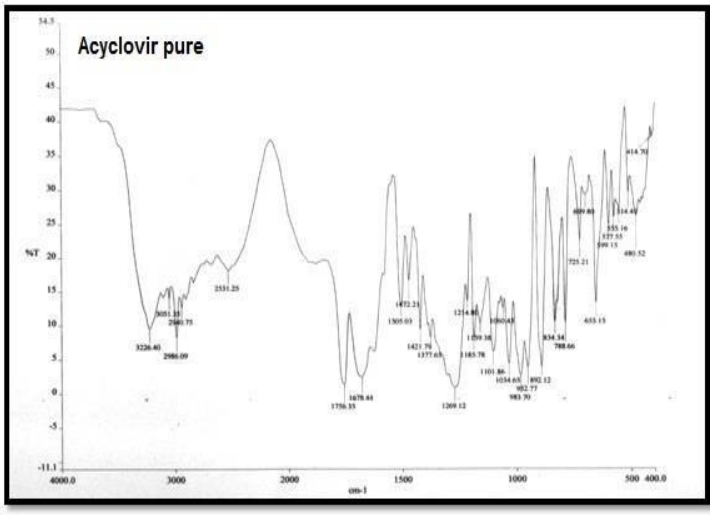
Table 14: concentration and absorbances of Acyclovir in 6.8pH phosphate buffer

Concentration	Absorbance
0	0
2	0.124
4	0.244
6	0.363
8	0.485
10	0.61
12	0.71

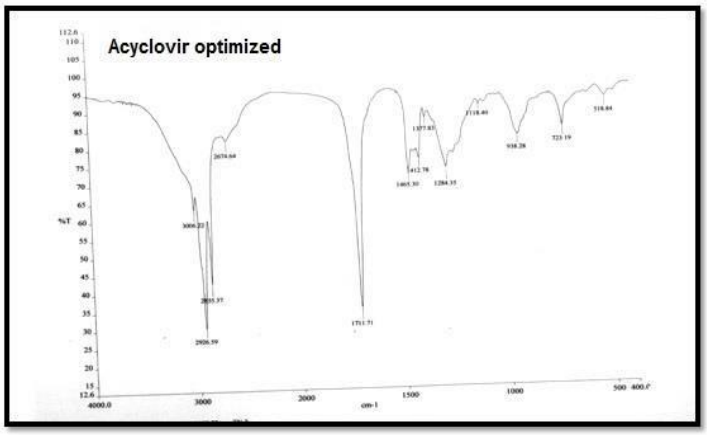


Graph 2 - calibration curve of Acyclovir

Drug And Excipient Compatibitlity



Graph 3 : FTIR Spectra of Acyclovir pure drug.



Graph 4: FTIR Spectra of Acyclovir optimized

Table 15: Preformulation parameters of Acyclovir tablets Prepared by direct compression method.

S.no	Formulations	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility index (%)	Angle of repose (^{0})	Hausner ratio
1	F1	0.45	0.52	24.6	13.4	1.15
2	F2	0.44	0.52	26.9	15.3	1.18
3	F3	0.45	0.51	24.2	11.7	1.13
4	F4	0.44	0.50	29.5	12.0	1.13
5	F5	0.45	0.52	20.6	13.6	1.15
6	F6	0.43	0.50	22.6	14.0	1.16
7	F7	0.66	0.8	25.6	16.66	1.2
8	F8	0.33	0.4	25.1	16.66	1.2

a. Bulk density and tapped density

Bulk density and tapped density of powder blend was evaluated. The results were shown in the Table No..

b. Angle of Repose

The angle of repose for the entire formulations blend was evaluated. The results were shown in the Table No. range from 11-16.

c. Compressibility Index

Compressibility index for the entire formulations blend was evaluated. The results were shown in the Table No., range from 20-27.

d. Hausner`s Ratio

The Hausner`s ratio for the entire formulations blend was evaluated. The results were shown in the Table No. , range from 1.15-1.20. All these are within the limit.

Evaluation Of Tablets

Hardness

The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 6.8 to 7.4 kg/sq cm. Shown in table no 16..

Friability

Friability values below 1% were an indication of good mechanical resistance of the tablets.

Weight Variation

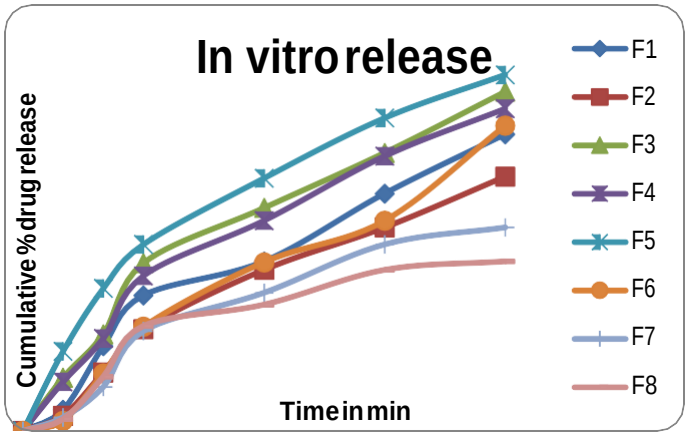
All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weight variation in all the Eight formulations was found to be 398 to 402 mg, which was in pharmacopoeial limits of ±5% of the average weight. Shown in table no 16.

Formula code	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content(%)
F1	7.2	398	0.26	99.6
F2	7.4	399	0.35	99.0
F3	7.0	400	0.28	99.4
F4	6.9	402	0.33	99.3
F5	6.8	398	0.28	99.2
F6	7.0	400	0.5	99.5
F7	7.2	401	0.45	99.8
F8	7.1	399	0.35	99.1

Table 16 : Post formulation parameters of tablets

Time in min	F1	F2	F3	F4	F5	F6	F7	F8
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
5	2.5	1.8	6.3	5.8	9.4	1.2	1.6	1.4
10	10	6.9	11.4	10.9	16.8	6.8	5.2	6.4
15	16	12	19.8	18.3	22	12.3	11.8	12.4
30	20	19	26.3	24.8	29.8	19.9	16.3	14.9
45	28	24	32.8	32.4	36.9	24.8	22	19
60	35	30	40	38	42	36	24	20

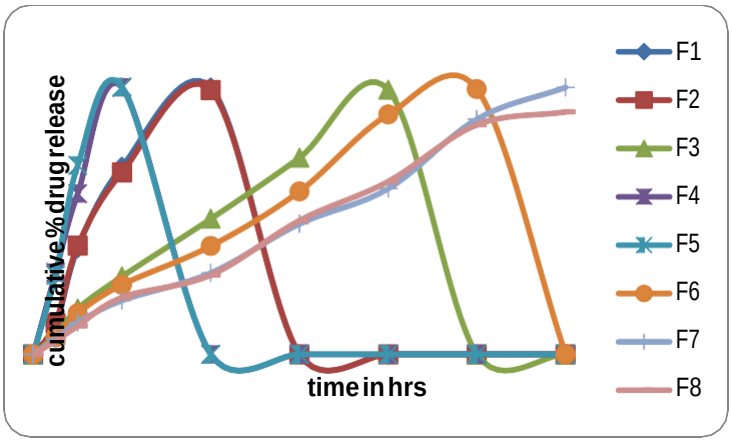
Table 17 : Dissolution Data For Core Tablet



Graph 5: Dissolution graph for core tablets.

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8
30min	10.6	11.6	7.2	30.6	29.7	6.3	5.7	5.0
1	39.8	40.7	17.1	60.2	70.8	15.4	11.9	10.6
2	70.3	68.2	29.2	100.1	100.3	26.1	20.2	21.4
4	100.1	99.1	50.8			40.6	30.5	29.7
6			73.7			61.1	48.9	50.2
8			99.26			89.9	62.1	64.8
10						99.5	88.2	86.1
12							100.1	90.9

Table 18: Dissolution Studies For Osmotic Tablets



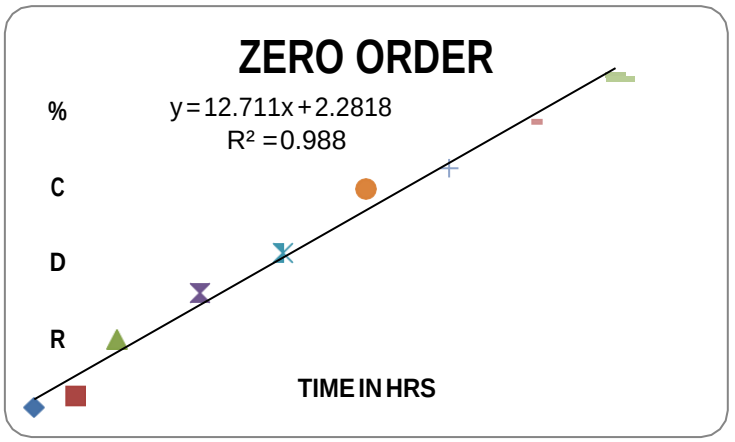
Graph 6: Dissolution graph for osmotic tablets

It is evident that after coating with semipermeable membrane of Cellulose acetate, the increase in concentration of osmogen NaCl leads to increase in drug release from the tablet due to the osmotic effect. Among all formulations F7 was optimized based on maximum drug release

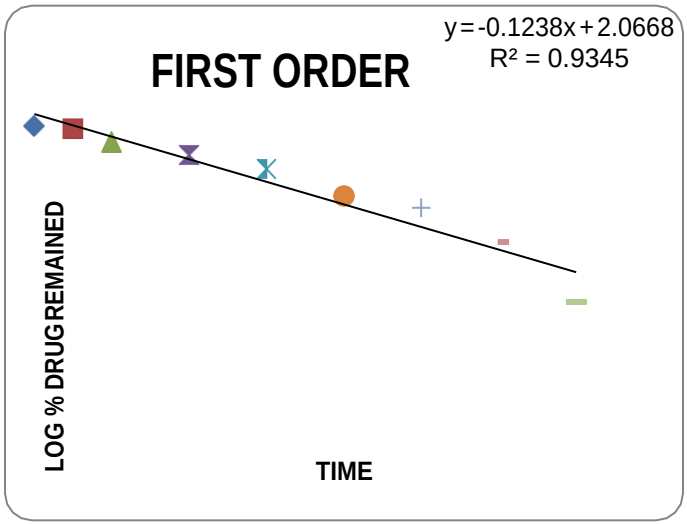
Kinetic Studies For Optimized Formulation (F7)

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	**8.218172043**	**0.129499236**	**29.32955731**	**1.792526468**
Intercept	**1.12327957**	**2.183959354**	**14.63931049**	**0.121415295**
Correlation	**0.9963709**	**-0.87381316**	**0.95978005**	**0.946105522**
R 2	**0.992754969**	**0.763549439**	**0.921177745**	**0.895115658**

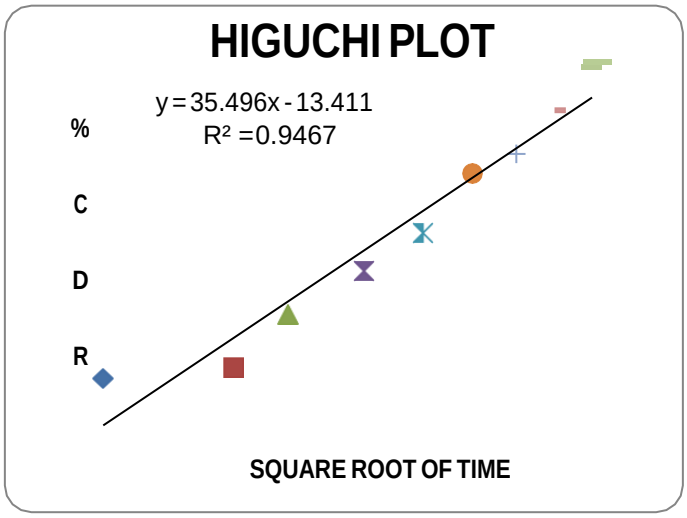
Table 19: Release kinetics for the optimized formulation F7



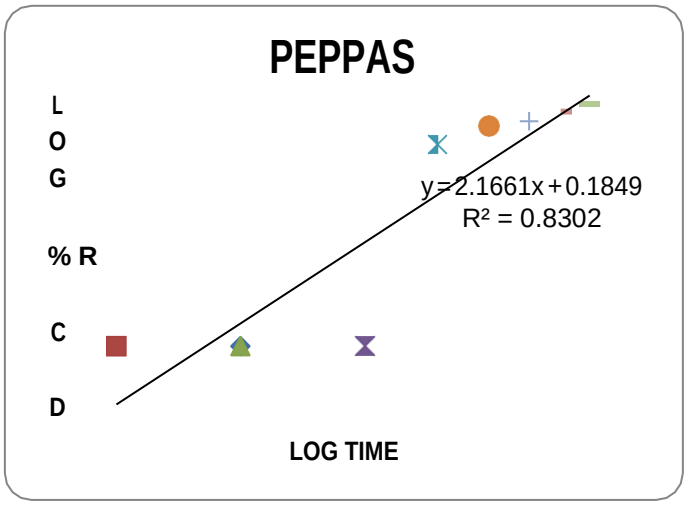
Graph 7: Zero order plot for optimized formulation



Graph 8: **First order plot for optimized formulation**



Graph 9 : **Higuchi plot for optimized formulation.**



Graph 10 : **Peppas plot for optimized formulation.**

Conclusion

- The following conclusion could be drawn from the research work carried out from the project:
- Osmotic tablets for acyclovir could be successfully prepared with different osmogens in different concentration and could be coated with semipermeable polymer like cellulose acetate for the release of the drug.
- In vitro release studies were carried out for all formulations to quantify percentage cumulative release of drug. Based on the drug release profile suitable formulation was selected. The Formulation no-7containing drug and NaCl with 1% has shown 100.1% of drug release in 12 Hrs and the drug release followed in zero order kinetics.
- Formulations of core tablets shown increased drug release rate with an increase in osmogen concentration.
- There is a good scope for the development of elementary osmotic pump system for this drug.

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