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## Osmotic release tablets formulation and evaluation of ace inhibitor molecule

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Article History	Abstract
<p>Received on: 17-01-2021 Revised On : 24-02-2021 Accepted on : 26-02-2021</p>	<p>In the present study the Suitable analytical methods were developed for the drug using UV – visible spectrophotometer. From the Preformulation study and thermal analysis (DSC), the interference was verified and found that the drug did not interfere with the excipient use. Core tablet was successfully prepared by wet granulation using Polyethylene oxide WSR N80, Mannitol 25C, silicon dioxide, magnesium stearate, Polyethylene WSR 303, sodium chloride, hydroxypropyl methylcellulose (HPMC E5), Iron oxide red. Isopropyl cellulose was found to be suitable granulating fluid for binder. Formulation of the drug coating was optimized by using 2<sup>2</sup> factorial design of experiment. The coated tablets were evaluated for various physicochemical parameter. About 79 to 95% of drug was released from the formulation A-E in 24 hr in 6.8 phosphate buffer. The in vitro drug release data were plotted in zero order kinetics and optimized batch were evaluated on the basis of regression coefficient. The in-vitro drug release from the optimized formulation in the dissertation was directly proportional to the concentration of plasticizer and concentration of cellulose acetate. The manufacturing procedure was standardized and reproducible.</p> <p><b>Keywords:</b> DSC, HPMC, A-E, UV.</p>
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### Introduction

For decades an acute disease or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms such as tablets, capsules, pills, creams, liquids, ointments, aerosols, injectables and suppositories. Presently, these conventional dosage forms are primarily prescribed pharmaceutical products. To achieve and to maintain the concentration of an administered drug within therapeutically effective range, it is often necessary to take drug dosage several

times a day. This results in fluctuating drug levels in plasma [1].

Ingestion is the traditionally preferred route of drug administration providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is a very little control over release of the drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses. Such situations, often results in constantly changing,

unpredictable, and often sub or supra therapeutic plasma concentrations leading to marked side effects [2]. Controlled drug delivery systems have been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage forms.

Therapeutically active molecules for the treatment and prevention of new existing diseases are currently being developed. Although pharmacological activity is the primary requirement for a molecule to be used as a therapeutic agent, it is equally important that the molecule reaches the sites of action, and hence drug delivery technologies have assumed importance. Scientists are pursuing the discovery and development of new molecules that have better absorptive and pharmacokinetic properties. Nevertheless (e.g. Short biological half-life). Drug delivery systems such as oral controlled release dosage forms, transdermal patches and implants are used to overcome these challenges. Although the cost of these drug delivery technologies is considerable, it is substantially less than the cost of developing a new molecule. Hence, a continued interest exists in developing novel drug delivery systems for temporal and spatial delivery of active agents [3].

#### Drug selection for oral controlled release drug delivery systems (OCRDDS)

The biopharmaceutical evaluation of a drug for potential use in controlled drug delivery system requires knowledge on the absorption mechanism of the drug from the G.I. tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH, and apparent partition coefficient.

#### Design and fabrication of OCRDDS

The majority of the oral controlled release systems are either tablets or capsules although a few liquid products are also available. The paucity of liquid sustained release mechanisms employed. Sustained release tablet and capsule dosage forms usually consists of two parts an immediately available dose to establish the blood level quickly and sustaining part that contains several times the therapeutic dose for protracted drug levels. More common methods that are used to achieve sustained release of orally administered drugs are as follows [9].

1. Dissolution controlled release systems
  - a) Encapsulation dissolution control
  - b) Matrix dissolution control
2. Diffusion controlled release systems
  - a) Reservoir devices

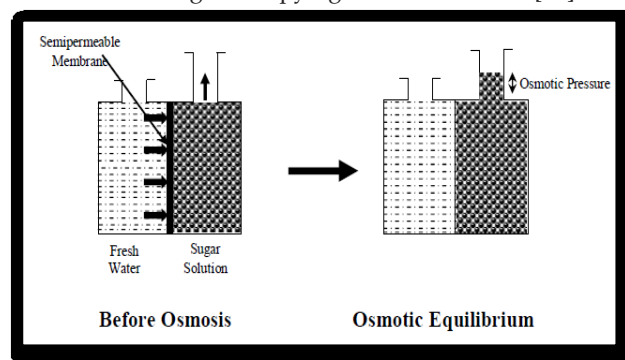
#### b) Matrix devices

3. Diffusion and dissolution controlled release systems
4. Ion exchange resins
5. pH dependent formulations
6. Altered density formulations
7. Osmotically controlled release systems

### Osmotic controlled drug delivery systems

#### Principle of osmosis

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semi-permeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure [10]. In 1748, Abbe Nollet first reported the osmotic process. In 1877, Pfeffer separated a sugar solution from water using a sugar-impermeable membrane and quantified the water transport. In 1884, Hugo de Vries invoked osmotic concepts to understand the contraction of the contents of plant cells placed in solutions of high osmotic pressure, where the cell membrane acts as a semi-permeable membrane. The osmotic pressure difference between inside and outside environments causes osmotic water loss and results in plasmolysis. In 1886, Van't Hoff identified an underlying proportionality between osmotic pressure, concentration, and temperature in Pfeffer's experiment. Later, he revealed a relationship between osmotic pressure and solute concentration and temperature that was similar to the ideal gas equation, where pressure is proportional to concentration and temperature. According to Van't Hoff's equation, the osmotic pressure in a dilute solution is equal to the pressure that the solute would exert if it were a gas occupying the same volume [10].



A schematic illustration of osmotic flow and attainment of osmotic equilibrium

Osmotic pressure, a colligative property, depends on the concentration of solute (neutral molecule or ionic species) that contributes to the 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 release rate of drug. Therefore, zero-order release, which is important for a controlled release delivery system when indicated, is possible to achieve using these platforms. In 1974, Theeuwes and Higuchi applied the principle of osmotic pressure to a new generation of controlled drug delivery devices with many advantages over other existing controlled drug delivery systems. The first of these devices, the elementary osmotic pump, is considered a typical delivery system that operates on osmotic principles.<sup>10</sup>

### Mechanism of Osmotic Controlled Release

#### Quantitative aspects of osmosis

Van't Hoff described the relationship between the osmotic pressure of a dilute solution and its concentration as follows:

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

Where,  $\pi$  = osmotic pressure in atmospheres

V = volume of the solution in liters

n = number of moles of solute

R = ideal gas constant, equal to 0.082 L·atm/mol·K

T = absolute temperature in K

The Van't Hoff equation also can be written as follows:

$$\pi = (n/V)RT \quad (2)$$

or

$$\pi = cRT \quad (3)$$

Where c is the concentration of the solute in moles per liter. The preceding equation can be applied satisfactorily to describe the osmotic pressure of dilute solutions of non-electrolytes such as sucrose and urea. Van't Hoff later observed that the osmotic pressure of electrolyte solutions were two, three, or more times greater than predicted by the general equation. Therefore, a factor *i* was introduced to account for the behavior of ionic solutions. The corrected equation for electrolyte solutions is written as follows:

$$\pi = icRT \quad (4)$$

By application of this equation, it is possible to calculate osmotic pressures for ionic solutions. Van't Hoff also observed that *i* approaches the number of ions as the molecule dissociates in an increasingly dilute solution.

Moreover, the deviations of concentrated electrolyte solutions from ideal behavior can be obtained from Raoult's law.

### Advantages of Osmotic drug delivery

Osmotic drug delivery systems for oral and parenteral use offer distinct and practical advantages over other means of delivery. The following advantages have contributed to the popularity of osmotic drug delivery systems [3].

- The delivery rate of zero-order (which is most desirable) is achieved with osmotic systems. Both in vitro and in vivo experiments have established this fact.
- Delivery may be delayed or pulsed, if desired.
- For oral osmotic systems, the drug release is independent of gastric pH and hydrodynamic conditions.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release rate of osmotic systems is highly predictable and can be preprogrammed by modulating the release control parameters.
- A high degree of in vivo-in vitro correlation (IVIVC) is obtained in osmotic system.
- The release from osmotic systems is minimally affected by the presence of food in the gastrointestinal tract (GIT) [11].

These advantages are attributed to the design of osmotic systems. Environmental contents (e.g. GIT fluids) do not gain access to the drug until the drug has been delivered out of the device. Osmotic systems have high degree of IVIVC, because the factors that are possible for causing differences in release profiles in in vivo and in vitro (e.g. variable pH, agitation) affect these systems to a much lesser extent [12].

### Osmotic pressure

The osmotic pressure  $\pi$  expressed in Eq. (6) directly affects the release rate. To achieve a zero-order release rate, it is essential to keep  $\pi$  constant by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure. For example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated

drug by producing an effervescent action in acidic media.

### Components of Osmotic Systems

The major formulation components of a typical osmotic delivery system include drug, osmotic agents, and a semi-permeable membrane.

### Osmotic components

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Osmotic agents can be any salt such as sodium chloride, potassium chloride, or sulfates of sodium or potassium and lithium. Additionally, sugars such as glucose, sorbitol, or sucrose or inorganic salts of carbohydrates can act as osmotic agents. Hydrophilic polymers encompass osmopolymers, osmogels, or hydrogels. These materials maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. The polymers may be formulated along with poly(cellulose), osmotic solutes, or colorants such as ferric oxide. Swellable polymers such as poly(alkylene oxide), poly(ethylene oxide), and poly(alkali carboxymethylcellulose) are also included in the push layer of certain osmotic systems. Further, hydrogels such as Carbopol (acidic carboxypolymer), Cyanamer (polyacrylamides), and Aqua-Keeps (acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polygluran) may be used. Finally, tableting aids such as binders, lubricants, and antioxidants may be added to aid in the manufacture of the osmotic systems [13].

### List of osmotic agents with their osmotic pressure

Compound or mixture	Osmotic pressure (atm)
Lactose : Fructose	500
Dextrose : Fructose	450
Sucrose : Fructose	430
Mannitol : Fructose	415
Sodium chloride	356
Fructose	355
Lactose : Sucrose	250
Potassium chloride	245
Lactose : Dextrose	225
Mannitol : Dextrose	225

Dextrose : Sucrose	190
Mannitol : Sucrose	170
Xylitol	104
Sorbitol	84
Dextrose	82
Citric acid*	69
Tartaric acid*	67
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribasic. 12 H <sub>2</sub> O	36
Sodium phosphate dibasic. 7 H <sub>2</sub> O	34
Sodium phosphate dibasic anhydrous	29
Sodium phosphate monobasic. H <sub>2</sub> O	28
Lactose	23
Fumaric acid*	10
Adipic acid*	8

\* Collected from article [14]

### Barrier layer formers

To restrict water entry into certain parts of the delivery system and to separate the drug layer from the osmotic layer, different materials are used as barrier layers. In a multilayered reservoir, the water-permeable coat consists of hydrophilic polymers. In contrast, water-impermeable layers are formed from latex materials such as polymethacrylate. Further, a barrier layer can be provided between the osmotic composition and the drug layer that consists of substantially fluid-impermeable materials such as high-density polyethylene, a wax, a rubber, and the like.

### Materials used in different layer formulations:

Component	Examples
Hydrophilic layer (water permeable)	Polysaccharides, hydroxyl propyl methyl cellulose, hydroxyl ethyl cellulose, poly(vinyl alcohol-co-ethylene glycol)
Water-impermeable layer	Kollicoat, SR latex, Eudragit SR
Barrier layer	Styrene butadiene, calcium phosphate, polysilicone, nylon, Teflon, polytetrafluoroethylene

### Oral osmotic pump:Multi Chamber Osmotic Pump:Push pull osmotic pump

Push pull osmotic pump is a modified EOP. 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 (the upper layer) contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. The drug layer accounts for 60-80% of the tablet weight while the osmotic polymer layer accounts for 20-40%. 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. When the system is placed in aqueous environment water is attracted into the tablet by an osmotic agent in both the layers. The osmotic attraction in the drug layer pulls water into the compartment to form in situ a suspension of drug. The osmotic agent in the non-drug layer simultaneously attract water into that compartment, causing it to expand volumetrically and the expansion of non drug layer pushes the drug suspension out of the delivery orifice.

### Formulation Parameters of Osmotic Drug Delivery System

#### a) Drug solubility

Drugs with high and low water solubility do not form a good candidate for osmotic delivery. Solubility modulators can be used to modify the solubility of drug particles. e.g.: Diltiazem hydrochloride, which is highly water soluble, is predominantly released by first order kinetic rather than zero order kinetics. So sodium chloride is used as solubility modulator so that 75% of drug is released by zero order kinetics other substance like cyclodextrins, effervescent mixtures etc are also used as solubility modulators.

#### b) Osmotic Pressure

Drugs selected as candidate for osmotic system, should possess Osmotic pressure as the release rate of drug from osmotic system is directly proportional to the osmotic pressure of the core formulation. If the drug does not possess sufficient osmotic pressure osmogens like NaCl,

Glucose, Sucrose, Glycine etc. is to be added in the core formulation to control the release of drug from the osmotic system.

#### c) Delivery Orifice

Delivery orifice is created in the osmotic system either by mechanical drilling or laser drilling in the semi-permeable membrane of the system. In case of CPOP the insitu pore formation take place depending on the concentration of the pore forming agent in the polymeric solution. The size of the delivery orifice has to be optimized. If a delivery orifice is too small the hydrostatic pressure may not be released causing deformation of the system or unpredictable drug release profile, while if delivery orifice is too large, diffusion of solute may take place.

#### d) Polymers used

The polymers used should be semi-permeable in nature. The polymers commonly used for this purpose are cellulose ester such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate and cellulose acetate butyrate. Swellable polymers are used in osmotic system for poorly soluble drugs. e.g. vinyl pyrrolidone, polyethylene oxide.

### Material and methods

#### List of material used in the study.

S. NO	Material	Manufacturer and supplier
1.	ACE inhibitor molecule	Wockhardt Pvt.Ltd.
2.	Polyethylene oxide WSR N80	Colorcon
3.	Polyethylene oxide WSR N303	Colorcon
4.	Sodium chloride	Signet Chemical Corporation, Mumbai
5.	Magnesium stearate	Signet Chemical Corporation, Mumbai
6.	Hydroxypropyl methylcellulose E5	Signet Chemical Corporation, Mumbai
7.	Polyethylene glycol 400	Signet Chemical Corporation, Mumbai
8.	Polyethylene glycol 3350	Signet Chemical Corporation, Mumbai
9.	Silicon dioxide	Evonik pharma polymers, Germany
10.	Cellulose acetate (CA 398-10)	Signet Chemical Corporation, Mumbai
11.	Polyethylene glycol	Signet Chemical

	6000	Corporation, Mumbai
12.	Acetone	Merck KGaA, Germany
13.	Isopropyl alcohol	Merck KGaA, Germany

## Experimental methods

### API Characterization:

#### Melting point

The melting point of the drug sample was determined by open capillaries using melting points apparatus.

#### Flow properties

**Bulk density:** Bulk density or apparent density is defined as the ratio of mass of a powder to the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another. The powder sample under test was screened through sieve no.18 and the sample equivalent to 25 g was accurately weighed and filled in a 100 ml graduated cylinder and the powder was leveled and the unsettled volume,  $V_o$  was noted. The bulk density was calculated by the formula:

$$\text{Bulk density } (\rho_o) = M/V_o$$

Where, M = Mass of powder

$V_o$  = Apparent unstirred volume

#### Tapped density

Tapped density was determined by using Electrolab USP Apparatus. The powder sample under test was screened through sieve no. 18 and the weight of sample equivalent to 25 g was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a nominal rate of 300 drops per minute for 500 times initially and the tapped volume  $V_o$  was noted. Tapping was proceeded further for an additional tapping for 750 times and tapped volume  $V_b$  was noted. The difference between two tapped volume was less than 2%, so  $V_b$  was considered as a tapped volume  $V_t$ . The tapped density was calculated by the formula:

$$\text{Tapped density } (\rho_t) = M/V_t$$

Where, M = weight of sample powder

$V_t$  = Tapped volume

#### Compressibility Index

Compressibility index is a measure of flow rate of powder. Compressibility index is a measure of relative importance of interparticulate interactions. The compressibility index and Hausner ratio are measures of the propensity of powder to be compressed. The

packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It is indicated as Carrs compressibility index (CI). The relationship between Compressibility Index and powder flow are given. The bulk volume and tapped volume was measured and compressibility index was calculated using the formula.

#### Hausner ratio

Hausner ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the apparent density. The relationship between Hausner ratio and powder flow are given the.

$$\text{HR} = \frac{\text{Tapped density}}{\text{Apparent density}}$$

#### Moisture content (LOD)

The moisture content of the drug was determined by using an Halogen Moisture analyser. Approximately 1 gm of drug was placed on the sample pan and kept at 105 °C and the LOD was read directly.

#### Hygroscopic studies

The study was conducted by exposing the drug to different humidity conditions at  $25 \pm 2$  °C with 33%, 53%, 75% and 94% relative humidity (%RH) for 7 days. The drug substance was kept in a petri plate and placed in desiccators containing different saturated solutions of salts as shown to obtain required RH.

Formulation Development

#### Core Formulation

The development of the formulation in the present study was mainly based on the system chosen and the drug selected. The push pull osmotic pump was selected for study. The solubility characteristics of the drug were considered more important in the development of formulations. The drug selected is highly soluble in water, osmotic pressure created by solution was assumed to be sufficient for its release through orifice. The formulation data were given.

#### Result and discussion

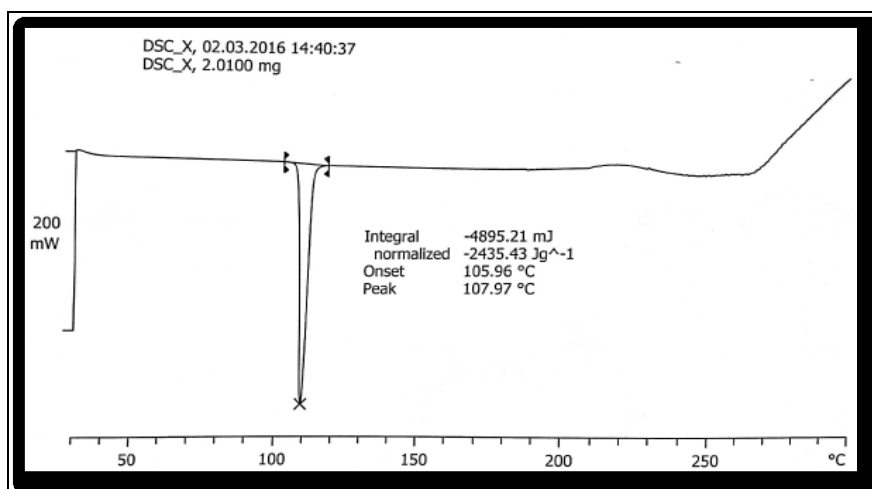
Push pull osmotic pump system was developed for an ACE inhibitor molecule drug with a view to deliver the drug in a controlled manner based on the principle of osmosis. The details of results and discussion were given in the following sections.

**Drug–excipient compatibility data for various excipients used in the study.**

Sr. No.	Ingredients	Initial	1 week	2 week	4 week
1	Drug	White powder	No change	No change	No change
2	Drug + mannitol 25C	White powder	No change	No change	No change
3	Drug + sodium chloride	White powder	No change	No change	No change
4	Drug + Iron oxide red	Reddish powder	No change	No change	No change
5	Drug + polyethylene oxide WSR N80	Off white powder	No change	No change	No change
6	Drug + Magnesium stearate	white powder	No change	No change	No change
7	Drug + Cellulose acetate-398-10	Off white powder	No change	No change	No change
8	Drug + Hydroxypropyl cellulose (HPC SSL)	Off white powder	No change	No change	No change
9	Drug + Polyethylene oxide WSR 303	Off white powder	No change	No change	No change
10	Drug + Hydroxypropyl methylcellulose(HPMC E5)	Off white powder	No change	No change	No change
11	Drug + Polyethylene glycol 3350	white powder	No change	No change	No change

**DSC studies**

The DSC studies were carried out to confirm the compatability of the excipients with the drug used in the formulation. The DSC scans for the pure drug and for mixtures of drug and different excipients are given. The data obtained from the DSC studies are reported in the Table 23.A perusal to the Table 23 indicates that there is no significant change in the peaks of drug-excipient mixtures in comparitision to pure drug, indicating that there is nocompatability of excipients with the drug.



DSC scan of ACE inhibitor molecule.API characterization:

**Flow properties**

The flow properties of the pure drug were determined and the data is reported in the **Flow properties of the drug**

Sr.No	Parameter	Result
1	Bulk density (gm/cc)	0.391 ± 0.050
2	Tapped density (gm/cc)	0.800 ± 0.025
3	Compressibility index (%)	51.042
4	Hausner's ratio	2.042

#### Moisture content (LOD)

The loss on drying of the pure drug sample was determined at 105° C and was found to be 1%L, which confirms the specification of suppliers COA.

#### Hygroscopic studies

Non - hygroscopic

Formulation Development:

#### Operation of Push pull osmotic pump

Before describing the formulation aspects of dosage form, it is necessary to understand the intended operational aspects of the dosage form. A push pull osmotic pump contains 2 layers in the core and a coating membrane. The core compartment is surrounded by a membrane consisting of a semi-permeable membrane forming polymer, and a plasticizer capable of improving film-forming properties of the polymers. The semi-permeable membrane forming polymer is permeable to aqueous fluid, but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane. After coming into contact with the aqueous fluids in the core, it will create osmotic gradient. The dissolved drug is released through the drilled orifice. Based on this consideration, suitable design of dosage form was attempted.

#### Composition of preliminary core formulations (F1 to F6)

DRUG LAYER						
Ingredients Qty (mg/tab)						
Batches	F1	F2	F3	F4	F5	F6
<i>Intragranular part</i>						
Drug	100	100	100	100	100	100
Polyethylene oxide WSR N80	218.5	30	128.5	188.5	108.5	158.5
Mannitol 25C	25	213.5	115	55	135	85
Silicon Dioxide	5	5	5	5	5	5
<i>Binder</i>						
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
<i>Extragranular part</i>						
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
<b>Total weight</b>	<b>350mg</b>	<b>350mg</b>	<b>350mg</b>	<b>350mg</b>	<b>350mg</b>	<b>350mg</b>
PUSH LAYER						
Ingredients Qty (mg/tab)						
Batches	F1	F2	F3	F4	F5	F6
<i>Intragranular part</i>						
Polyethylene oxide WSR N303	90	90	30	90	90	90
Sodium chloride	50.75	50.75	90.75	50.75	50.75	50.75
Hydroxypropyl methylcellulose E5	7.5	7.5	27.5	7.5	7.5	7.5
Iron oxide red	1	1	1	1	1	1
<i>Binder</i>						

Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
<i>Extragranular part</i>						
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75
<b>Total weight</b>	<b>150mg</b>	<b>150mg</b>	<b>150mg</b>	<b>150mg</b>	<b>150mg</b>	<b>150mg</b>
<b>Drug layer + push layer</b>			<b>500 mg</b>			

In these formulations IPA was used as binder solvent, Mannitol 25C & sodium chloride as osmogen, magnesium stearate were used as lubricant. In formulation F6 silicon dioxide is used as added excipients. As mentioned in the prior procedure the drug and silicon dioxide were sifted together properly so as to increase the surface area and reduce the interaction between drug particle. These formulations were compressed with 10.3 mm round standard concave punches. The precompression properties of the granules were reported in Table 26 and the parameters evaluated for the core tablets are given in the

#### Precompression parameters for the formulations F1 to F6

Parameter	F1	F2	F3	F4	F5	F6
Loss on Drying (%)	0.80	0.98	0.85	0.99	0.87	0.70
Bulk density (gm/ml)	0.391	0.330	0.335	0.399	0.402	0.391
Tapped density (gm/ml)	0.800	0.780	0.820	0.855	0.842	0.802
Compressibility index (%)	51.042	51.440	51.998	52.651	51.665	51.862
Hausner ratio	2.042	2.000	2.065	2.622	3.011	2.013

#### Parameters of the core tablets of formulations F1 to F6

Parameter	F1	F2	F3	F4	F5	F6
Uniformity of weight (mg) <sup>#</sup>	500 ± 2.93	500 ± 2.79	500 ± 2.76	500 ± 4.61	500 ± 2.83	500 ± 2.90
Hardness (N) <sup>*</sup>	120 ± 2.00	117 ± 0.05	110 ± 2.30	115 ± 2.03	121 ± 2.13	114 ± 2.07
Thickness (mm) <sup>*</sup>	5.8 ± 0.02	5.9 ± 0.06	5.7 ± 0.02	5.8 ± 0.15	5.8 ± 0.25	5.9 ± 0.18
Friability (%) <sup>#</sup>	0.09	0.22	0.02	0.20	0.30	0.15

<sup>#</sup> Results of one batch

<sup>\*</sup> Each value was an average of six determinations

#### In-vitro drug release study of the preliminary batches

Dissolution was carried out as per the procedure mentioned in materials and methods chapter. The details of the dissolution study for the tablets of formulations F1 to F6 are given. 8% & 10% weight gain were obtained from the coating and the dissolution profile was checked.

#### Release profile of preliminary batches

(Hr)	F1		F2		F3	
	8%	10%	8%	10%	8%	10%
1	5.90%	2%	0.19%	0.13%	9.80%	6.60%
2	12.40%	9.80%	3.06%	2.85%	38.10%	19.20%
4	32.50%	30%	9.70%	8.06%	50.30%	44.10%
6	68.50%	48.70%	15.06%	12.10%	72.45%	63.10%

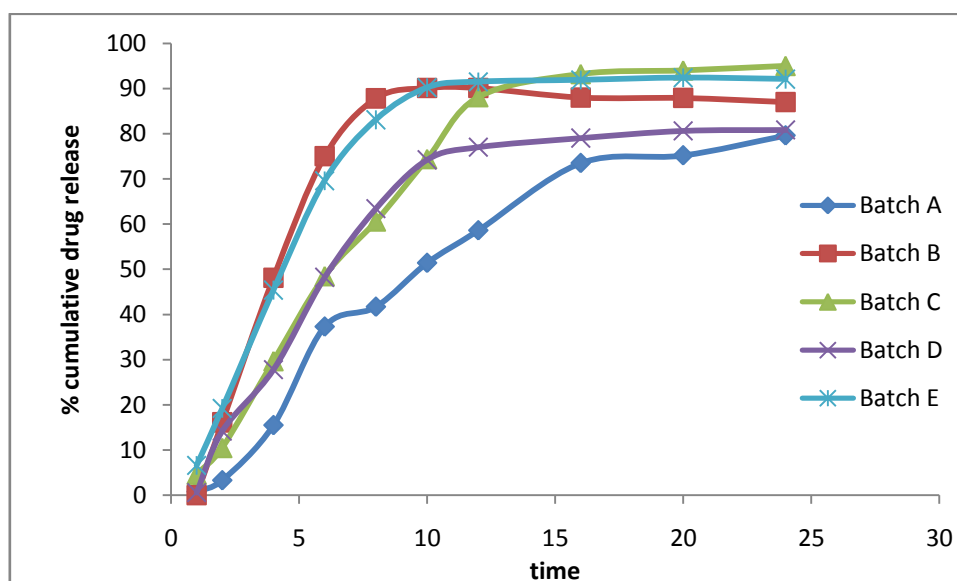
8	76.60%	64.10%	20.50%	17.93%	84.13%	83.10%
10	77.70%	82.30%	33.48%	25.66%	86.20%	90.40%
12	77.36%	77.40%	38.63%	29.60%	87.70%	91.20%
16	80.20%	77.40%	56.98%	49.30%	86.80%	91.70%
20	81.40%	77.53%	59.45%	51.55%	89.40%	90.40%
24	78.30%	82.80%	57.23%	51.96%	89.89%	89.96%

(Hr)	F4		F5		F6	
	8%	10%	8%	10%	10%	12%
1	5.80%	0.00%	8.30%	0.00%	4.60%	5.20%
2	22.90%	14.70%	27.50%	6.40%	10.50%	9.30%
4	57.20%	35.90%	60.80%	30.70%	29.70%	25.70%
6	79.20%	57.80%	87.60%	51.00%	44.50%	40.40%
8	83.80%	74.00%	91.90%	81.60%	60.60%	55.20%
10	85.60%	79.10%	90.30%	87.70%	74.40%	69.60%
12	85.50%	76.80%	89.30%	88.80%	88.10%	58.50%
16	86.30%	77.10%	89.40%	89.90%	93.20%	88.70%
20	85.10%	78.20%	85.30%	89.01%	94.00%	89.50%
24	85.20%	76.45%	86.50%	90.04%	95.00%	89.80%

Out of all the preliminary batches (F1-F6); F6 batch showed the maximum release. Hence F6 batch was considered as final core formulation batch for the statistical method analysis.

### In-vitro drug release study

The *in-vitro* drug release studies were carried out as per the procedure mentioned in the materials and methods chapter. The data obtained from the dissolution studies for the formulations is recorded. A perusal it is evident that the drug release was found to be in the range of 79 to 95% for the formulations in 24 h. This indicates that the drug release was consistent for all the formulations. The effect of Polyethylene glycol 3350 and Cellulose acetate-398-10 concentration on the drug release was clearly indicated in the release studies. The drug release was found to be decreased at lower levels of PEG 350 and CA-398-10; while the release shows zero order in formulation batch C for 12 hrs due to optimum amount of plasticizer.



Comparative dissolution profile of Trial A – E

- Batch C was considered as the optimum batch as it shows the maximum release of 95% and the highest  $r^2$  value.
- From the tested batch of A-E the obtained dissolution profile were evaluated for zero order release kinetics/ characteristics. For extended release type of dosage form the rate & the extent of release are two important things to be considered.
- From the batches A-E we have observed that some batches were good at extent of drug release & some batches were good at rate of drug release
- Considering the gastric transition time we evaluated the batches for zero order kinetics upto 12 hrs.

### Summary & conclusion

The conclusions drawn from present investigation are as follows: The summary & conclusion arrived in this study indicated that the push pull osmotic pump of the ACE inhibitor molecule developed in this investigation was found to produce a controlled release of the drug for 24 hours. Further studies were needed to investigate this formulation for its performance in vivo and its bio equivalence. Thus the objectives envisaged in this thesis were arrived.

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