Research Article

Formulation and Evaluation of Controlled Porosity Osmotic Tablets of Valsartan

P. S.N. Sri Bala*, Muskan, Hameeda Begum, Mohammed Arsalan, Madiha Jabeen, Dr. Anupama Koneru.
Sultan-UL-Uloom college of pharmacy, Hyderabad-500034, Telangana, India.
***Corresponding author's E-mail:** sribalapatkar@gmail.com

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ABSTRACT

In an osmotic drug delivery system, the medication is released from the system by solvent influx across the semipermeable membrane, and the membrane then delivers the drug outside through a laser-drilled orifice. Along both sides of the semipermeable membrane, osmotic and hydrostatic differential pressure control how much fluid enters the system. A controlled release valsartan formulation would extend the time it takes for valsartan to reach an optimum concentration in the body because its half-life is roughly 5-8 hours. With the help of this system, the dosage can be reduced to 160 mg while still actively being released for 12-hours. Low water solubility of valsartan prevents the creation of the osmotic pressure required to cause drug release. In order to improve solubility and its osmotic pressure, anhydrous disodium hydrogen orthophosphate was used in this study. Other excipients encompass osmogents such as NaCl, microcrystalline cellulose as a texturizer, PVP K-30 as binder, talc and magnesium stearate are used as diluents in the formulation, coating agents like ethyl cellulose, propylene glycol that helps absorbing extra water and PEG 400 as a pore forming agent. Drug identification by FTIR, preformulation studies, standard curve preparation, in-process and final product evaluations, in-vitro dissolution studies, and stability studies were expertly carried out. The best-formulated tablet among the various formulations releases 92.35% of the API in 12 hours. The integrity of the developed tablets was demonstrated by FT-IR studies in conjunction with stability studies. Controlled Release tablets were compressed without problem and therefore do not require any alteration to the ratio of excipients in the formulation.

Keywords: osmotic drug delivery system, osmogents, formulation, controlled release, valsartan.

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INTRODUCTION

Osmosis

Osmosis is the Latinized version of the now-outdated word osmose. Osmotic, which means "pertaining to or of the character of osmosis," is a derived word. For instance, osmotic pressure is a type of pressure that arises from or is related to osmosis. Osmosis is the tendency of water to cross a semipermeable membrane from a hypotonic solution (a solution with a low concentration of dissolved chemicals) to a hypertonic solution (a solution with a high concentration of dissolved compounds).[1] Osmotic pressure, which controls how the drug is delivered from the osmotic device, is created when fluid from the external environment is ingested into the dosage form. The osmotic pressure produced by the osmogen's consumption of fluids directly correlates with the rate at which medication is distributed from an osmotic pump [2].

Osmotically controlled drug delivery systems

Osmotic pressure drives these systems, which regulate the release of medications. Of all the drug delivery methods, osmotic medication delivery is the most intriguing and well-liked. Numerous patents have been issued and in-depth research on osmotic systems has been conducted [3]. Alza was a pioneer in the development of osmotic medication delivery systems, and in addition to owning the majority of the patents under review, it also sells a number of medications with an osmotic basis. These devices can be used for both parenteral and oral administration. Oral osmotic systems are used in therapeutic procedures for the digestive tract. Parenteral osmotic medication administration is carried out using implanted pumps. ALZA Corporation was the first business to develop osmotic medicine delivery systems. A zero-order profile is used to administer the medication [4].

An osmotically dispersion formulation includes:

1. A water-permeable membrane forming a portion or all of the enclosure's walls

2. An activated agent.

3. An additive that exhibits an osmotic pressure and is known as an osmotic attractant.

When used in an aquatic setting, the active component and movable partition combine to osmotically draw water into the enclosure, causing it to distend and swell and release the medication into the environment through the

orifice. The pace of medicine release can be changed by adjusting the gradient of osmotic pressure. [5]

Advantages:

There are various numbers of advantages of OCDDS which have been listed below

Deliveries can be delayed or pulsed if desired.

➢ Stomach acidity or hydrodynamic circumstances have little impact on drug release.

➢ They are well-defined and comprehended.

➢ Improve the oral bioavailability and lowers the dose dependent toxicity

➢ The discharge mechanisms are not drug-dependent.

➢ There is a strong correlation between in-vitro and in-vivo measurements in osmosis systems.

➢ The relatively constant availability of water in GIT justifies this strategy at least in terms of the amount required to activate and control osmotically based technologies.

➢ The osmotic system release in the digestive tract is not significantly influenced by food.

➢ The osmosis system's rate of release may be controlled by changing the discharge control parameters because it is highly predictable.[6]

Disadvantages:

➢ OCDDS has shown significant clinical benefits in a variety of therapeutic areas. Some systems have improved patient compliance, while others have reduced the side effects of others and have reduced the side effects of their active ingredients. Some OCDDS limitations, however, have been reported.

➢ Expensive

➢ If the coating process is not well controlled, there is a risk of film defects leading to dose dumping.

➢ The hole size is critical.

➢ Drug dumping.

➢ In the event of unexpected adverse events, retrieval therapy is not possible.[7]

Factors affecting drug release rate

Solubility:

To enhance drug release, APIs for osmosis delivery should be soluble in water in the required range. Moreover, by adjusting the solubility of these pharmaceuticals within the core, it is possible to obtain efficient release patterns for medications that would otherwise seem to be poor candidates for osmotic delivery.[8]

Solubility-modifying approaches:

➢ The use of swellable polymers38 produces constant rate medication release since polyethylene oxide and vinyl acetate copolymer have comparable swelling rates.

➢ Use of wicking agents: These agents may increase the drug's surface area when in contact with incoming aqueous fluids. For instance, sodium lauryl sulphate, colloidal silicon dioxide, and so forth. The same osmotic technique is used by Ensotrol@ technology to administer medications.

➢ Using effervescent mixtures: The releasing rate is controlled by this method's employment of a citric acid and sodium bicarbonate mixture to create pressures in the osmotic system.

Use of cyclodextrin derivatives40: It has been demonstrated that these substances increase the medication's absorption, which is not particularly high. Osmotic systems can be used to explain the same occurrence.

➢ Alternative salt form: A change in salt form may affect solubility.

➢ Use of encapsulated excipients: A solubility modifier excipient in the form of a mini-tablet coated with a rate-controlling membrane is used.

➢ Approach to Resin Modulation: Ion-exchange resin techniques are frequently employed to alter the solubility of APIs. Among the resins employed in osmotic systems are pentaerythritol, citric, adipic, and poly (4-vinyl pyridine).

➢ The use of excipients that may alter the crystal habit of the medicine can be utilized to modulate solubility since different crystal forms of the drug may have varying degrees of solubility.

➢ Through a variety of processes, including saturation solubility and pH-dependent solubility, excipients can be utilized to modify the solubility of APIs. Organic acid, buffering agents, and other such excipients are examples.[9]

Osmotic pressure:

From the equation :

F (z) I-s/p……(11)

Where

S = Solubility of the drug.

F(z) Release of the drug in zero order kinetics.

P = Density of core tablet.

So, according to the equation, the rate of drug release from an osmotic system is proportional to the osmotic pressure of the core formulation. If a semipermeable membrane separates a solution from pure water or two solutions with

different drug concentrations, the tendency to equalize concentration will result in the inflow of water from the solution with the lower drug concentration to the other end[10]. As a result, optimizing the osmotic pressure gradient between the inside compartment and the external environment is critical. The Van't Hoff equation can also be used to calculate osmotic pressure.

x = CRT……(12)

Where:

It = Osmotic pressure of the solution.

C = Molar concentration of the solute in the solution.

R = Gas constant.

T= Absolute temperature.

A few trial calculations have shown that the osmotic pressure of the saturated solution of even moderately soluble compounds is very high and of the order of several hundred and even thousands of pounds per square inch of pressure. If the desired osmotic pressure is not obtained, a second compound known as an osmotic attractant agent is incorporated into the enclosure with the active agent. Osmotic attractants are derived from compounds such as:

a. Experiencing high osmotic pressure.

b. Never degrade

c. Avoid interfering with the membrane or the enclosed wall.

d. Avoid interfering with the way the active medication molecule works or the environment it is eventually released into.

e. Do not quickly deteriorate.

Size of delivery orifice:

In order to minimize drug delivery by diffusion through the orifice and achieve the ideal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than the maximum size[11]. Additionally, the area needs to be sufficiently large, above a minimum size, to reduce the system's buildup of hydrostatic pressure. Osmotic pumps typically have orifice sizes between 600B and I mm. An osmotic tablet coating can have a delivery orifice by using the following techniques:

- Mechanical drill
- Laser drill: Tablets can be made with holes that are less than a millimeter in size using this technology. For drilling, a CO_2 laser beam (with an output wavelength of 10.6 g) is typically used because it offers high reliability at a reasonable price.
- Indentation made in core tablets using modified punches with a needle on the upper punch is not covered by coating. The coating procedure leaves the TW indentation susceptible, providing a pathway for release in the osmotic system.
- The semipermeable coating encompasses leachable components, like a controllable porosity osmotic pump.

Type and quantity of plasticizer:

Hard and brittle polymers can be toned down and made more malleable by plasticizers, increasing their tolerance to mechanical stress. The rate at which of absorption of drugs from osmotic tablets can be impacted by the permeability of the polymer films[12].

MATERIALS AND METHODS

Valsartan was a gift sample from bright labs (Hyderabad, India). All compounds were of an analytical grade.

Formulations of valsartan core tablets

Wet granulation was employed to make the valsartan core tablets, and a batch size of 20 tablets was maintained. Valsartan used as an Active pharmaceutical ingredient (API), sodium chloride used as an Osmogent, anhydrous disodium hydrogen orthophosphate acting as a solubilizer, and microcrystalline cellulose were all weighed in adequate quantities. PVP K-30 (binder) was dissolved in IPA in the required quantity. To achieve the required size of granules, the prepared binder solution was added to the powder mixture to create a dumpy mass. To eliminate moisture, the granules were heated at a temperature of 50 to 55°C for 60 minutes. Weighed and blended with granules were the required amounts of diluents such as talc and magnesium stearate. Using a compression machine with 10 mm standard concave on both sides, the powder mixture was compressed into round tablets (300 mg each). On a Monsanto tablet hardness tester, the compression force was altered and modified to produce tablets with a hardness of about 5 kg cm^{-2} [13].

The table (1) lists the three different valsartan osmotic core tablet formulations and their variable osmogenes concentrations: -

Table 1: Formulation details of core of CPOT of Valsartan.

Ingredients	C-1	C-2	C-3
Drug	80	80	80
Sodium chloride	40	80	120
Anh. Na2HP04	30	30	30
MCC	105	65	25
PVP K-30	40	40	40
Magnesium stearate	2.5	2.5	2.5
Talc	2.5	2.5	2.5
Total weight	300	300	300

Coating of valsartan tablets

The required level of ethyl cellulose used as a semi-permeable membrane was precisely weighed and then dissolved in the recommended amount of IPA acting as a

solvent. Propylene glycol was added in the necessary amount to the aforementioned solution, and the combination was agitated to produce a clear solution. A specific amount of PEG 400 acting as a pore-forming agent was blended. Table 2 lists the ingredients in the coating solution that was utilized to coat the valsartan tablets. A stainless steel, 10 cm pear-shaped spray coating pan with baffles was used to hold the valsartan core pills. Warm air was circulated through the tablet bed as the coating pan was rotated at 20–25 rpm. Once exit air reached 28 °C , the coating procedure was initiated. Spraying of coating solution was done at a rate of 2-3 ml/min while maintaining an atomizing air pressure of 30 to 35lb/in^2. By maintaining the inlet air temperature at 45 - 50 °C, the outlet temperature was kept between 28 and 30 °C. The coating process was carried out until the necessary weight gain (10%) was achieved. Before further evaluation, tablets were always dried at 50 °C for 2 hours[14].

The table below lists the three different coating solution composition and their variable pore-forming agents:

Table 2: Formulation details for coating solution of CPOT of valsartan.

Ingredients	C-a	C-b	C-c
Ethyl cellulose	2.631 mg	2.489mg	2.347mg
PEG-400	0.142ml	0.284ml	0.426ml
İPA	100 ml	100 ml	100ml
Propylene glycol	2ml	2ml	2ml

Nine different formulations of valsartan-controlled porosity tablets were prepared using different concentrations of Osmogent (C-1, C-2, C-3) and pore-forming agent (C-a, C-b, C-c) as F1, F2, F3, F4, F5, F6, F7, F8, F9.

Formulation of F1, F2, F3 for COPT of valsartan

All the formulations Fl, F2, and F3 have the same core composition i.e., contain drug: Osmogent in 1: 0.5 ratio but differ in their coating compositions i.e., the amount of pore-forming agent is 5.39%,11.5%,18.15% weight of semipermeable membrane respectively. All the tablets are coated to a weight gain of 10% of their initial weight(300mg) i.e., to 330 mg.

Formulation of F4, F5 and F6 for COPT of valsartan

All the formulations F4, F5, and F6 contain the same core composition i.e., have drug Osmogent in ratio but differ in their coating compositions i.e., have a pore-forming agent in 5.39%,11.5%, and 18.15% weight of semipermeable membrane respectively. All the tablets are coated to 10% of their initial weight (300mg) i.e., to 330mg.

Formulation of F7, F8, F9 for COPT of valsartan

All the formulations F4, F5, and F6 contain the same core composition i.e., have drug Osmogent in a 1:1.5 ratio but differ in their coating compositions i.e. have a pore-forming agent in 5.39%,11.5%, and 18.15% weight of semipermeable membrane respectively. All the tablets are coated to 10% of their initial weight (300mg) i.e., to 330mg.

Table 3: Formulation details of F1, F2, F3,F4,F5,F6,F7,F8and F9.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
CORE									
DRUG	80	80	80	80	80	80	80	80	80
Sodium chloride	40	40	40	80	80	80	120	120	120
Anh.Na2HP04	30	30	30	30	30	30	30	30	30
MCC	105	105	105	65	65	65	25	25	25
PVP K-30	40	40	40	40	40	40	40	40	40
Mg. Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
COAT									
Ethyl cellulose	2.631	2.489	2.347	2.631	2.489	2.347	2.631	2.489	2.347
PEG 400	0. 142	0.284	0.426	0. 142	0.284	0.426	0.142	0.284	0.426
IPA	100	100	100	100	100	100	100	100	100
Propylene glycol	2	2	2	2	2	2	2	2	2

All the above formulations were prepared as tablets by wet granulation technique, followed by punching them into tablets by compression machine and coating them with a semipermeable membrane having leachable pore-forming agents in a spray.

Evaluation Test for Valsartan

The following are the various evaluation parameter to be tested for controlled porosity osmotic tablets of valsartan

- Angle of repose
- Bulk density

- Tapped density
- Carr's index
- Thickness
- Hardness
- Friability
- Weight uniformity
- Determination of drug content
- In- vitro Dissolution studies
- Reproducibility
- Curve fitting analysis
- Effect of pH on drug release
- Effect of agitation intensity on drug release
- Scanning electron microscopy (SEM)
- Stability studies

Each of the individual parameters will be discussed further in detail as follows.

Pre-Compression Studies

Flow properties of granules:

1. Angle of repose: The funnel method was used to calculate the granules, angle of repose. Granules that had been precisely weighed were placed in a funnel. The tunnel's height was modified such that the funnel's tip just touched the top of the pile of granules. As the granules flowed freely through the funnel and onto the surface, the diameter of the powder cone was measured and the angle of repose was calculated using the equation below.

Tan Θ = h/r

where the powder cone's height and radius are denoted by h and r, respectively.

2. Bulk density: The tapped bulk density (TBD) and the loose bulk density (LBD) were both calculated. 2 g of the powder from each formula, which had been previously lightly shaken to break up any agglomerates, was added into a tapping density device, with the tappings set to 25 per minute. Once there was no longer any loudness change, the tapping was stopped. The following equations were used to calculate LBD and TBD. Powder weight divided by packing volume is known as LBD.

TBD = weight of the powder/tapped volume of the packing.

3. Carr's index: The Carr's index of the powder was determined by using the formula:

Carr's index (%) [(TBD — LBD) x 100]/TBD

Where TBD is the total bulk density and LBD is the loose bulk density[15].

Post Compression Studies

Evaluation of Porous Osmotic Pump Tablets

1. Thickness: Using a screw gauge, the thickness of the coated and core tablets was measured. Each formulation's 10 tablets were chosen at random and used. Millimeters are used to measure the thickness.

2. Hardness: The Monsanto hardness tester was used to gauge the hardness of the coated tablets and the core tablets. Each formulation's 6 tablets were chosen at random and used. Both the standard deviation and the average hardness were computed. It is stated as $Kg.cm^{-2}$.

3. Friability: The microporous osmotic pump tablets matrix and core tablets friability were assessed. Randomly choose 10 tablets, weigh them, and then put them in the Roche friabilator. For four minutes, the device was rotated at 25 rpm. The tablets were cleaned and weighed again after the revolutions. The formula, that helps in calculating percentage friability is given below,

$$\%Friability = \frac{Initial\,wt.\,of\,tablets\ -\ Final\,wt.\,of\,tablets}{Initial\,wt.\,of\,tablets} \times 100$$

4. Weight uniformity: From each batch, 10 tablets were taken at random and weighed separately. The standard deviation of 20 pills was computed using the average weight of the ten tablets.

5. Determination of drug content: Ten tablets were precisely pulverized and weighed, accurately measured amounts of the powder containing 100 mg of Valsartan were extracted in 100 ml of methanol by shaking for 20 minutes. Before being spectrophotometrically examined at 250 nm, samples were filtered through Whatmann filter paper no. 1 and adequately diluted with methanol. The calibration curve of Valsartan in methanol was used to calculate the amount of medication present[16].

***In Vitro* Dissolution Studies**

Using a USP-type 1 dissolution device, the drug samples were tested for in vitro drug release (basket type). 37 + 0.5^0C was kept as the ambient temperature. One Valsartan-coated tablet was placed in a dissolution basket and was dipped into the dissolution beaker containing 900 nil of dissolution medium, 0.1 N HCl 1.2pH. The basket-type apparatus was allowed to run for 120 minutes at 50 rotations per minute. 5 ml of samples were withdrawn every 15,30,1,2 hrs. using a micro syringe. After sampling samples were filtered through 10 gm filter paper. Every time, the same amount of the sample was added to the fresh dissolution medium (37°C). Collected samples were analyzed at 250 nuts using 0.1 N HCl as a blank. Then the dissolution medium was changed to 6.8 PBS and the same procedure was carried out for the next 10 hrs. i.e., continued up to 12 hrs. total. The cumulative drug release percentage (% CDR) was examined and analyzed.. Release profiles of various formulations were compared. The developed formulations were subjected to various tests[17].

Reproducibility: The Reproducibility of the manufacturing procedure was confirmed by preparing two repeat batches (batch size of 20 tablets each) of the final optimized formulation on two different occasions. The tablets were evaluated for dissolution as the rest of the parameters were proved to be reproducible and compared with tablets of the earlier batch

Curve fitting Analysis: To determine the kinetics of medication release from the microporous, osmotic pump tablet. Zero-order, first-order Higuchi models were used to examine the in vitro release data.

1. Zero-order release kinetics:

The release data was modeled using the equation below to analyze the zero-order release kinetics:

Q, the amount of drug released, K_0, the zero-order release rate constant, and t, the release duration, are all factors in the equation

$dq/dt = K_0$.

The graph shows the cumulative drug release percentage (% CDR) over time.

2. First-order release kinetic:

To analyze the first-order release kinetics, the release rate data are fitted into the following equation:

$dQ/dt = K_1 Q$

Where K_1 is the first order release rate constant, t is the release time, Q is the fraction of medication released, and the graph is drawn with time and log% CDR remaining.

3. Higuchi release model:

To analyze the Higuchi release model, the release rate data are fitted into the following equation:

$Q = KH\ t_{1/2}$

Where Q is the drug release fraction, KH is the release rate constant, and t is the release time. The graph is plotted as % CDR versus the square root of time[18].

Effect of pH on drug release

The effect of pH on drug release is investigated in the optimized formulation of microporous osmotic pump tablets. The best formulations are undergone dissolution studies the effects go, 6.8 pH phosphate buffer and pH change method (where the buffers are changed at selected time intervals) in the rotation speed of 50 rpm and 37 ± 0.5°C using USP dissolution test apparatus (type 2) and are compared.

Effect of agitation intensity on release of drug

A release study was performed using USP type II dissolution apparatus (paddle type) rotational speeds of 50, 100, and 150 in PBS pH 6.8 to investigate the effect of dissolution medium agitational intensity (rpm). Samples were analyzed at 250 nm. Percentage cumulative drug release was calculated.

Membrane morphology of porous osmotic pump tablet - scanning electron microscopy

To elucidate the mechanism of drug release, coating membranes of Valsartan tablets were subjected to scanning electron microscope (SEM) studies before and after dissolution studies. The tablets were cut with a sharp blade before dissolution, and the coating membrane was removed. This membrane was used for SEM after being cleaned with a dried cloth to remove any adherent particles. Similarly, after 24 hours of dissolution study, the coating membrane was removed from the tablets and used for SEM. To remove any adherent solid particles, the coating membrane was carefully washed 3-4 times with water. The coating membrane was dried overnight in a tray dryer at 45^0C. A scanning electron microscope was used to examine the membrane after it had been coated with gold-palladium in an argon atmosphere[19].

Stability studies

According to ICH, the International Conference of Harmonization guidelines, the formulation was subjected to accelerated stability studies to provide evidence on the quality of a drug substance or drug product that changes over time under the influence of various environmental factors, such as temperature, humidity, and light. Valsartan 10 mg tablets were packed in 0.04 min thick aluminum foil strips laminated with PVC[20]. For one month, the packed tablets were stored in ICH-certified stability chambers at 40 + 2°C and 75 + 5% RH. After one month, the samples were withdrawn and examined for changes on the coating membrane (i.e. change in color, appearance of spot, any kind of microbial or fungal growth, any bad odor, smoothness).Samples were evaluated for hardness, drug content and for in vitro drug release too[21].

RESULTS AND DISCUSSION

Pre-formulation studies

Valsartan was subjected to the following preformulation tests and has passed all the tests

1.FT-1R Spectrum (Fourier transform infrared spectrum)

The Fourier transform infrared spectrum of pure valsartan drug was compared to the physical mixture of formulation as well as the valsartan. Peaks in the wave number region were seen for both the physical mixtures of valsartan and polymers as well as the distinctive functional groups of pure valsartan. Alkane C-H stretching: 2983.04 cm^{-1}, 2923.02 cm^{-1}; bonded Hydroxyl bending: 1209.32 cm^{-1}, 1384.25 cm^{-1}; aromatic secondary amine N-H bending: 1105.80 cm^{-1}, 1112.25 cm^{-1}; 1198.42 cm^{-1},1105.04 cm^{-1} (Aromatic tertiary amine) C-N tremor There were no peaks that clearly emerged or simply disappeared. This illustrates that the drug and the used polymers don't interact pharmaceutically. Peaks within the predicted range testify to the validity of the study's materials and the lack of any interactions.

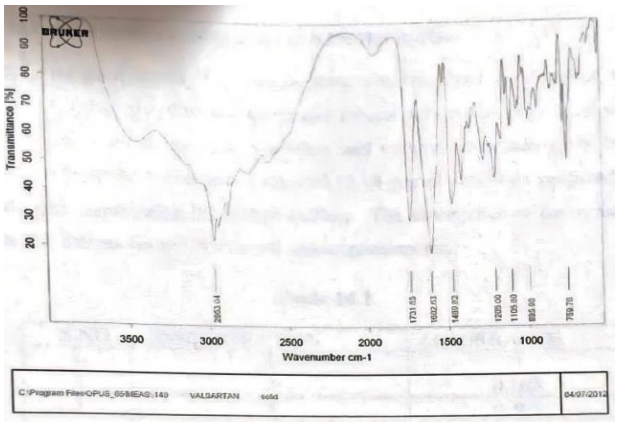


Figure 1: FT_IR spectrum of pure valsartan drug

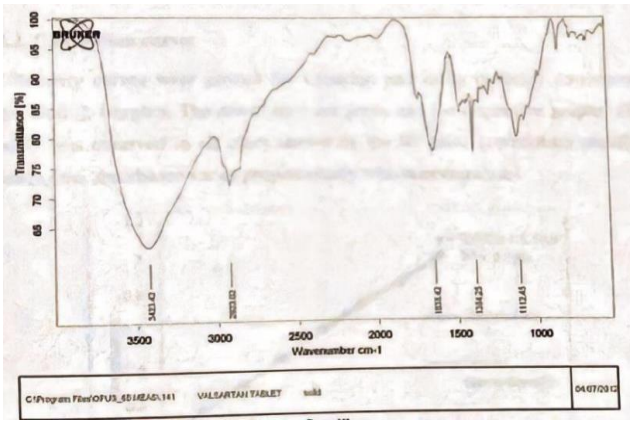


Figure 2: FT_IR of CPOT physical mixture

Analytical Development

A) Standard Graph of Valsartan in 0.1N HCl Buffer:

10 mg of valsartan drug was accurately weighed and dissolved in 10 ml of methanol (1000µg.ml^{-1}). 1ml was taken and volume was increased to 10m1 with 0.IN Ho (l00 µg.ml^{-1}). 1ml was taken and volume was increased to 10m1 with arc HCI (10µg.ml^{-1}). There are 2,4.6.8.10,12,14µg.ml^{-1} solutions prepared from that. Further dilutions were performed with 0.1 N NCI buffers. A UV-visible spectrophotometer was used to measure the absorbance of the solutions at 250 nm.

B) Calibration curve:

The calibration curves for valsartan were plotted at various concentrations ranging from 2-14µg.ml^{-1}. The absorbance is given, as well as the corresponding graphs. The R^2 value (correlation coefficient) demonstrated perfect linearity in all cases, indicating that absorbance varies proportionally with concentration.

C) Standard Graph of Valsartan in 6.8 Phosphate Buffer:

The medication 10 mg of valsartan was precisely measured and dissolved in 10 ml of methanol (1000µg/ml). After taking 1 ml, 10 m1 of 6.8 phosphate buffer (100 µg/ml) were added. From 1 ml of 6.8 pH phosphate buffer (10µg/ml), a volume of 10 m1 was created. prepared from solutions containing 2,4,6,8,10,12,14,16,18 and 20 µg/ml. Additional dilutions were made using 6.8 pH phosphate buffers. A UV-visible spectrophotometer was used to measure the solutions' absorbance at 250 nm.

D) Calibration curve:

Valsartan calibration curves were plotted at various concentrations ranging from 2-14µg.ml^{-1}. The absorbance and corresponding graphs are provided. In all cases, the R^2 value (correlation coefficient) demonstrated perfect linearity, indicating that absorbance varies proportionally to concentration.

Pre-Compression Studies

Evaluation of flow properties of granules:

The powder flow properties for the drug and Excipients Physical Mixture was performed and following results were obtained.

Table 4: Angle of repose, Bulk density, Tapped density, Carr's index, Hardness, Friability, Thickness, weight and Drug content for all the formulations .

Formulation code	Angle of repose	Bulk density	Tapped density	Carr's index	Hardness (kg/cm²) (n=10)	Friability (%) (n=10)	Thickness (mm) n=5	Weight (mg) (n=20)	Drug content %
F1	29.13±0.03	0.387±0.006	0.438±0.005	11.64±0.005	5.12±0.11	0.445	3.32±0.003	300±1.61	99.11±0.616
F2	29.01±0.12	0.365±0.003	0.430±0.0 2	15.11±0.006	5.05±0.02	0.466	3.45±0.002	301±1.12	98.54±0.735
F3	28.78±0.11	0.378±0.002	0.433+0.004	12.70±0.002	4.96±0.17	0.566	3.51±0.012	300.6±1.41	99.16±0.438
F4	26.51±0.34	0.373±0.004	0.436±0.002	14.44±0.009	4.84±0.18	0.631	3.58±0.014	300.1±2.13	99.36±0.592
F5	25.91±0.49	0.386±0.002	0.431±0.003	10.51±0.004	4.77±0.14	0.633	3.47±0.052	301±1.11	99.19±0.561
F6	25.67±0.53	0.371±0.004	0.436±0.003	14.67±0.008	4.69±0.21	0.666	3.57±0.061	300±1.32	99.54±0.372
F7	27.18±0.57	0.368±0.003	0.434±0.002	15.20±0.004	4.39±0.30	0.598	3.61±0.007	300.5±1.85	99.65±1.549
F8	26.57±0.16	0.371±0.004	0.433±0.006	14.31±0.008	4.52±0.17	0.631	3.54±0.017	300±1.62	99.96±0.997
F9	27.62+0.34	0.369±0.004	0.430±0.004	14.18±0.006	4.13±0.24	0.642	3.63±0.071	300+1.74	99.67±0.761

From the table (4), we can get the following data and conclude as follows:

Angle of repose: The angle of repose desirability for the granules of various Formulation codes lie in the range of 25.67±0.53 -29.01±0.12 % which indicates that they have GOOD flow properties as per I.P.

Bulk density : The bulk density desirability for the formulations lie in the range of 0.365±0.003 - 0.387±0.006 gm/ml which values can be used in determination of Carr's index for powder flow properties.

Tapped density : The tapped density desirability for the 9 formulations range from 0.430±0.002 -0.438±0.005 gm/ml which can be used in determination of Carr's index.

Carr's index : The Carr's index values are calculated for determining compressibility of the granules which in turn indicate the flow properties which lie in the range of 10.51±0.004 - 15.11±0.006 % which indicates that the physical mixture has excellent flowability.

Post Compression Studies

Physical Characterization of Controlled Porosity Osmotic Tablets of Valsartan:

Physical characterization of the prepared CPOT of valsartan can be done both for the core of the tablets and coated tablets.

From the above table (4), Thickness of the coated tablets were in the range of 3.44+0.13-3.72+0.017mm, Hardness was slightly increased due the coating of the tablets and were found to be in a range of 4.38±0.163-5.34±0.11 kg/cm2 and all the tablets were had a weight gain of 10% (30mg) of their initial weight for coating process which were found to be in a range of 330-331 mg.

Determination of Drug Content:

From the above table (4), we can see that the drug content values found to be between 98.54+0.735-99.96+0.997

In-Vitro Dissolution Studies:

The USP type ll (spinning paddle) dissolution apparatus was used to conduct the in vitro dissolution investigation.. The first two hours of dissolution was carried out in 0.1N HCl buffer (pH 1.2) and the next ten hours was carried out in a 6.8 phosphate buffer. The dissolution medium volume was kept to 900ml and the dissolution duration was out for a total of 12 hrs. At regular intervals of time 5 ml of the dissolution fluid was collected using a syringe and the same amount of the medium was replaced. The temperature was maintained at 370C and the paddle was rotated at 50 rpm. The withdrawn samples were analyzed spectrophotometrically in an UV-Visible spectrophotometer at 250 nm to obtain the % drug release at that particular time interval which can be summarized as follows.

Table 5: % Cumulative drug release of the trial osmotic tablets at different time intervals.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	3.42	4.61	6.22	15.32	17.67	20.17	34.18	35.16	40.34
2	6.01	7.98	9.89	23.26	26.76	31.45	50.67	52.91	56.89
3	1 1.41	14.56	16.73	36.26	40.43	40.41	59.95	60.43	69.11
4	19.69	27.88	31.74	45.69	47.12	49.91	67.97	70.66	79.64
6	31.62	46.91	49.99	61.28	65.41	61.59	76.97	85.96	89.01
8	46.81	57.81	61.01	68.32	70.99	76.78	87.91	94.11	
10	57.85	67.33	70.16	74.36	77.69	87.37	96.79	99.74	
12	64.79	71.97	79.04	80.12	83.12	92.35	105.75	107.91	

F1:

From the table, it can be concluded that at the end of the 12th hr. Fl trial tablets release about 64.7% of the drug from the dosage form. But it can be seen that at the end of 2 hrs. only 6% of the drug is released, which is not a suitable criterion for formulating as a Controlled release formulation. This phenomenon may be accounted for due to the low concentration of osmotic agent used(0.5% of the total drug concentration) and low amount of pore-forming agent (5.39% of the semi-permeable membrane amount used). Thus, the drug release needs to be further modified.

F2:

F2 trial tablets release about 71.97 % of the drug from the dosage form which is more when compared to Fl trial tablets. It can be accounted for due to formation of more pores on the tablets as the pore forming agent concentration is 1 1.5% of the surface of concentration of semipermeable membrane used. But at the end of 2 hrs the tablet releases only 7.98% of the drug in the buffer (in vivo simulation of stomach pH) which is not desirable. So, the drug release has to be further modified.

F3:

From the table we can see that F3 trial tablets release 79.04% of the drug which is better when compared to Fl and F2 trial tablets as the concentration of pore forming have been further increased to 18.15% of the amount of

semipermeable used. As a result , more amount of the drug is released from the formulation. But it can be seen that only 9.28% of the drug is released in 2 hrs which is not a suitable criterion. Thus, the drug release pattern is needed to be modified.

From all the data obtained for the 3 trial formulations Fl, F2, F3 it can be seen that the drug release increases with the increase in the concentration pore forming agent where the concentration of osmotic agent is kept constant.

F4:

From the table, it can be seen that %CDR increased when compared to F3 formulation at the end of 12th hr. which was found to be 80.12. This can be accounted for due to the increase in the concentration of osmotic agent to the drug in a 1:1 ratio. It can also be seen that at the end of 2 hrs F4 trial tablets released 23.26% of the drug which is a better release compared to the previous 3 formulations. But the drug release pattern can be further modified to get a better formulation.

F5:

F5 trial tablets released 83.12% of the drug from the osmotic tablets at the end of 12th hr which is a better release compared to F4 trial tablets. This can be accounted to the increase in concentration of the pore forming agent as the concentration of osmotic agent was kept constant. In order to get even better release another formulation of F6 is prepared.

F6:

In order to get a better release pattern compared to F5, F6 formulations have been prepared and their release patterns have been studied which released 92.35% of the drug from the osmotic tablets at the end of 12th hr. This was a very good release pattern as it also released 31.45% of the drug at the end of 2nd hr. This release pattern can be accounted for by the increase in the concentration of pore forming agent when compared to F5 formulation.

In all the above 3 formulations i.e., F4, F5, and F6 the drug release pattern increased with an increase in the concentration of the pore-forming agent.

F7:

From the table it can be seen that F7 formulation releases 105.75% drug at the end of 12thhr. It can be attributed for the increase in concentration of osmotic agents used i.e.in 1:1.5 ratio of the drug. Moreover, it releases about 50% of the drug within 2hrs of its initial release which is not a suitable characteristic of a controlled release formulation.

F8:

F8 formulation releases about 107.91% of the drug at the end of 12thhr and about 52.91% at the end of 2nd hr which is not at all a desired characteristic of a controlled releases formulation. This phenomenon can be attributed to both the increased concentrations of osmotic agents and pore forming agents compared to F6 formulation. Moreover, the osmotic tablet showed the slight cracks of the coat on the surface of the tablet during the dissolution process which is not desirable.

F9:

F9 formulation trial tablets could not release the drug for 12hrs as the tablet busted after 8hrs of dissolution which is not at all desirable for formulating it as a controlled porosity osmotic tablet. Tablet bursting was seen due to the increased pressure of the osmotic agent which the tablet could not retain and as a result got busted as the pores formed were not sufficient to release the drug from the formulation.

All the above 3 formulations F7, F8, F9 %CDR increased with an increase in the concentration of pore forming agents. From the above results it can be concluded that as the concentration of osmotic agent and pore forming agent increases drug release from the dosage form also increases.

Curve Fitting Analysis:

The in vitro release data was fitted to various kinetic models like First order, Zero order and Higuchi. In porous osmotic pump tablets, all the formulations from FI to F6 followed zero order kinetics, F7, F8 and F9 follows Higuchi release model. Results are given in the following table. When the data were plotted according to the first-order equation, the formulations showed a comparatively poor linearity, whereas the regression value for zero-order equation was 0.9851(highest among all the formulations from FI to F6), which indicated that drug release from formulation F6 was independent of drug concentration and thus it can be selected as the best formulation from the various prepared controlled porosity osmotic tablets.

Table 6: various regression coefficient (R^2) values for zero order, first order and Higuchi

Formulation	0 order	1st order	Higuchi
F1	0.9504	0.8404	0.8798
F2	0.9703	0.7841	0.9023
F3	0.9772	0.7571	0.9133
F4	0.9265	0.5546	0.9086
F5	0.9165	0.5278	0.9139
F6	0.9851	0.5273	0.8912
F7	0.8624	0.4157	0.9915
F8	0.8495	0.4137	0.9879
F9	0.8476	0.5142	0.9917

Thus, by performing in vitro dissolution studies and curve fitting analysis F6 formulation can be selected as the best formulation among the various prepared formulation trial tablets for controlled porosity osmotic tablets of valsartan

Effect of % weight gain on drug release

To study the effect of weight gain by coating on drug release, core tablets of valsartan of the batch F6 were

coated with the same coating composition so as to get tablets with different weight gain (8,10,12% w/w). The release profile of valsartan from these formulations is shown in the following graph. It is clearly evident that drug release decreases with an increase in weight gain of the coating membrane. No bursting of the tablet was observed during the dissolution in any formulation.

Effect of pH on Drug Release

When formulation F6 was subjected to in vitro release studies with different pH no significant difference in the release profiles were seen compared to that in pH change method (where first 2hrs of dissolution was carried out in pH 1.2 buffer followed by pH 6.8 buffer for next 10hrs). Thus, the fluid in different parts of the GI tract will scarcely affect release from the osmotic system.

Effect of Agitational Intensity on Drug Release

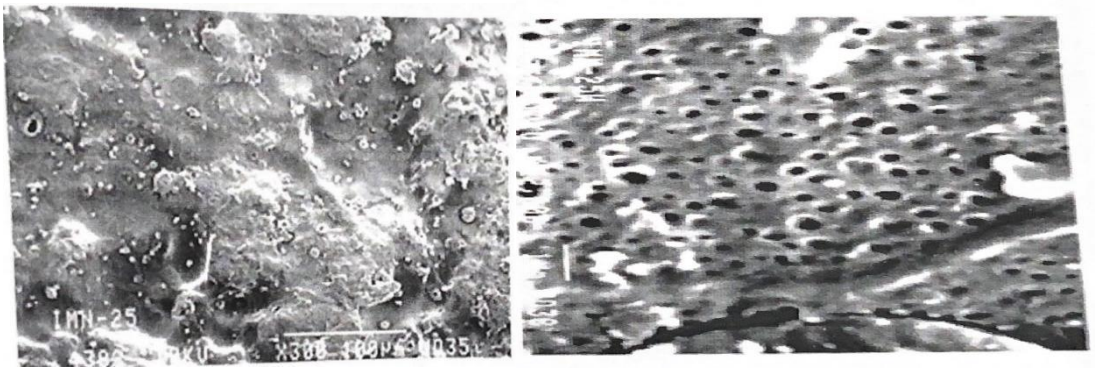
The following graph shows that the release profile of valsartan from the developed formulation F6 is fairly independent of the agitational intensity of the release media and hence, it can be expected that the release from the developed formulations will be independent of the hydrodynamic conditions of the body.

Reproducibility

Batch to batch uniformity is very much essential for obtaining reproducible results. In Order to verify this, the tablets of the batch F6 were formulated for another two times. Release studies were conducted as specified for in vitro study and similar release profiles were obtained. Following graph demonstrates that the formulating procedure is reproducible.

Scanning Electron Microscopy (SEM)

Clarifying the modifications is necessary. The membrane structure underwent SEM examinations (both prior to and following dissolution testing). SEM micro graphs of the coating membrane (before and after dissolution) are shown in Figure A and B. It was anticipated that pores would develop following dissolution. Because it portrays before dissolution, pores are evident as tiny spots in Figure (A). Figure(B) illustrates that pores created following dissolution were clearly visible and numerous. Additionally, the coating surface gets rougher due to leaching after dissolution. The pore-forming substance, PEG-400, is thought to have leached from the membrane, causing it to become porous. Finally, it is feasible to conclude that leaching of PEG-400 from the membrane caused the membrane to become porous, allowing medication release to occur. Pore counts were directly related to in proportion with the amount of pore former being removed from the membrane. On the basis of this, it can be said that the tablets created for this experiment were controlled porosity osmotic tablets.



A B

Figure 3: SEM micro graphs of coating membrane of F6 formulation containing 18.15% W/V volume of PEG 400 in coating solution A) Before dissolution and B) After dissolution.

Stability studies

Tablets of F6 formulation were kept for stability studies by storing them for 1 month in a stability chamber maintained at 400C at 75% RH. The samples were checked for any changes in physical properties after one month. It was seen that the surface lacked any alterations in color or the appearance of any form of spots. The absence of any microbial, fungal, or offensive odor growth on the surface was also detected. The texture of the tablets remained unchanged.

Stability study of F6 performed at 0 and 1 month of formulating the COPT of valsartan:

At 0 days

Hardness (kg/cm^2) - 4.85±0.15,

Weight variation (mg) -330.2±1.05

Content uniformity (%) - 99.54±0.372.

After 1 Month

Hardness (kg/cm^2) - 4.98±0.05

Weight variation (mg) -330±1.07

Content uniformity (%) - 99.36±0.287

Comparatively it was observed that the tablets from the optimize batch continued to mimic the same release pattern after a month of storage with no changes to their physical characteristics or drug release profiles.

CONCLUSION

valsartan was effectively incorporated into a controlled porosity osmotic pump-based medication delivery system for the efficient management of hypertension by covering the core tablet with absorbable pore-forming chemicals the creation of micro-porous tablets was sped up and made less expensive by doing away with the need for pricey laser drilling based on the study's findings F6 was determined to be the best formulation overall since it releases 92.35% of the medicine in 12 hours drug release from the porous osmotic tablets was inversely linked to coat weight but directly proportional to the concentration of pore former and osmotic agent the PH and hydrodynamic parameters of the body were discovered to have an impact on drug release from the proposed formulations the number of pores that develop depends on the initial amount of porosity in the membrane and is studied by SEM once the membrane comes into contact with an aqueous environment different kinetic models were adapted to accommodate the in vitro drug release the zero-order graphs regression values were closer to one formulation process that was standardized and proven to be reproducible which indicated that the system under development followed zero order ease kinetics after a month of storage under accelerated stability conditions developed formulations were determined to be stable.

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