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Advancements in Controlled Drug Delivery: A Focus on Controlled Porosity Osmotic Drug Delivery Systems

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ABSTRACT
The limitations of conventional drug delivery systems often lead to suboptimal therapeutic outcomes and potential toxicity. In response to that, Osmotic drug delivery systems (ODDS) are one type of controlled drug delivery device that has been developed and shown potential. ODDS utilizes osmotic pressure for controlled and sustained drug release, maintaining therapeutic levels independent of pH and dissolution medium. Controlled porosity osmotic pumps (CPOP) represent a notable advancement in ODDS technology. These systems consist of a drug core surrounded by a semipermeable membrane, which, upon contact with water, forms micropores, regulating drug release over time. This review provides insights into osmosis, CPOP technology, components, and evaluation methods, aiming to enhance understanding and development of efficient therapeutic interventions.

KEYWORDS: Osmosis, Controlled drug delivery, osmotic pump, pore former

I. INTRODUCTION

For decades, drug treatment has heavily relied on pharmaceutical dosage forms, with oral administration being the preferred route due to its convenience. However, conventional oral delivery often falls short in controlling drug release and maintaining optimal concentrations at the target site. Factors like drug properties and gastrointestinal conditions further complicate drug bioavailability.[1]

To overcome these challenges, alternative routes like parenteral administration have gained attention for their precision and avoidance of gastrointestinal issues. Recent pharmaceutical research has thus concentrated on innovative delivery systems to enhance therapeutic outcomes.[1]

The objective of drug development is to optimize molecules for sustained efficacy and improved patient experience, aiming for consistent blood levels, enhanced bioavailability, and reduced side effects. Various strategies, including matrix, reservoir, and osmotic systems, have been employed to achieve controlled drug release.[2]

This review explores advancements in novel drug delivery, focusing on mechanisms, benefits, and applications for improved therapy and patient adherence. By delving into these innovative approaches, it offers insights into the future of drug delivery research and its clinical implications.[2]

OSMOSIS

Osmosis is the phenomenon wherein solvent molecules move between a semipermeable membrane that separates an area with a greater solute concentration from a region with a lower solute concentration. This process plays a pivotal role in controlling drug delivery systems. Osmotic pressure regulates the release of drugs from osmotic devices. It is produced when fluids from the external environment enter the dosage form.

The osmotic pressure caused by fluid absorption by osmogens directly affects the speed at which osmotic pumps administer drugs.Remarkably, osmotic pressure is an invariant of solute particle concentration since it is a colligative feature of solutions. Consequently, variables including solution solubility, molecular weight, and activity coefficient affect how quickly medications are released via osmotic delivery systems.[3]

PRINCIPLE OF OSMOSIS

The initial documentation of osmotic effects traces back to Abbenollet's observations in 1748, while Pfeffer pioneered the first quantitative assessment in 1877. Pfeffer's experimental setup involved utilizing a selectively permeable membrane that allowed water passage but hindered sugar diffusion, segregating apure water and sugar solution. Consequently, a unidirectional flow of water occurred into the sugar solution until counteracted by an applied pressure, denoted as π. Pfeffer demonstrated that this osmotic pressure, π ,

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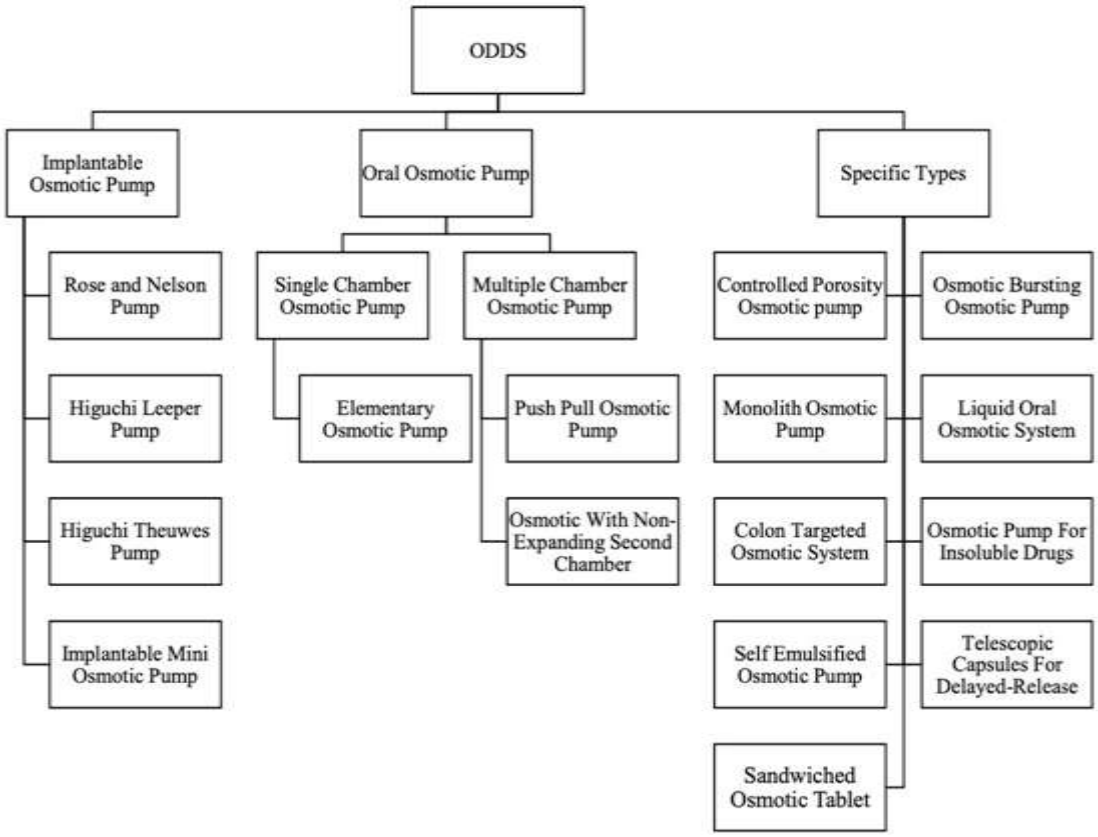
exhibited a direct correlation withthe concentration of the solution and the temperature absolute.[3]

Shortly thereafter, Vant Hoff elucidated the congruence between these findings and the principles governing ideal gas behavior. He formulated an expression akin to the ideal gas laws:

$$\pi = \Phi\ c\ r\ t$$

In this expression,Φ = osmotic pressure gradient
c = sugar concentration in the solution
r = gas constant
t = absolute temperature.

Vant Hoff's work established a foundational link between osmotic phenomena and fundamental physical laws, paving the way for deeper understanding and application in diverse scientific domains.[3]



THE CONTROLLED POROSITY OSMOTIC PUMP (CPOP)

With water-soluble leachable pore-forming chemicals included into the membrane, CPOP is an advanced osmotic tablet invention. This coating for a semi-permeable membrane is applied carefully using the right coating process. The CPOP is a type of dosage form that can include one or more compartments. It consists of a membrane with an asymmetric structure enclosing the medication, which is supported by a porous substructure. One feature that sets the CPOP design apart is that drug release is not facilitated by traditional apertures, but rather by pores that are created in situ during operation within the semi-permeable wall. Small amounts of water-soluble additives seep out of the water-permeable polymer materials when exposed to water, resulting in the creation of a sponge-like structure inside the walls with regulated porosity. Drug breakdown within the core functionally starts.

The mathematical expression for the water flow rate into the device is as follows.[4]

$$dv/dt = Ak/h\ (d\pi - dp)$$

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Where,
dv/dt = waterflow rate into system
k = membrane permeability
A = surface area
dπ = osmotic pressure gradient
dp = hydrostatic pressure gradient between membrane.

ADVANTAGES OF (CPOP) TABLETS

1. Consistent drug release, characterized by zero-order kinetics following an initial delay.
2. The potential for delayed or pulsatile drug delivery.
3. Drug release remains unaffected by physiological variables such as gastric pH, hydrodynamic conditions, or specific drug characteristics.
4. Enhanced in vitro-in vivo correlation, ensuring reliable drug delivery performance.
5. Elevated drug release compared to conventional systems.
6. Minimal interference with drug release in the presence of gastrointestinal food contents.
7. Predictable and customizable drug delivery rates facilitated by CPOP.
8. Elimination of the need for laser drilling due to in situ pore formation.
9. Streamlined production scalability.
10. Mitigation of stomach irritation issues through uniform surface drug delivery.
11. Versatility in accommodating a wide range of drug solubilities, including substances that are water soluble, partially soluble in water, and insoluble in water.[4]

LIMITATIONS OF (CPOP) TABLETS

1. High preparation costs may pose a barrier to widespread adoption.
2. Lack of control over therapy retrieval in case of unexpected adverse events.
3. Potential risk of dose dumping due to inadequate coating process control.
4. Possibility of drug tolerance development, impacting long-term efficacy.[4]

The fundamental structure of osmotic pump tablets with controlled porosity typically includes the following components:

1. **Core tablet:** This serves as the main reservoir for theadditional excipients and the active pharmaceutical ingredient (API). It is often composed of the API, fillers, binders, and disintegrants. These fillers and binders serve various purposes, such as providing bulk to the tablet, aiding in tablet compression, improving tablet disintegration, and enhancing drug release characteristics. The selection of specific fillers and bindersbased on variables like the API's characteristics,desired tablet characteristics, and manufacturing requirements.[5,6.]

Table 1: Examples of various fillers and binders.

Fillers	Binders
1.Microcrystalline cellulose (e.g., Avicel) 2. Lactose 3. Dicalcium phosphate 4. Mannitol 5. Calcium carbonate	1. Hydroxypropyl cellulose (HPC) 2.Hydroxypropylmethylcellulose (HPMC) 3. Polyvinylpyrrolidone (PVP) 4.Starches (e.g. Pregelatinized starch) 5. Ethyl cellulose

Semipermeable membrane: This membrane, which encircles the core tablet, selectively allows water to pass through it but not the dissolved API or other excipients. It controls the rate of water influx into the tablet. These excipients can be used alone or in combination to tailor the permeability and mechanical properties of the to attain the required drug release profile, use a semipermeable membrane. The selection of specific excipients based on elements including the drug's solubility, desired release kinetics, and compatibility with other tablet components.[5,6.]

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Table 2: Examples of various polymers used for semi permeable membrane.

Polymers used for semi permeability mechanism
1. Cellulose acetate 2. Cellulose acetate butyrate 3. Ethyl cellulose 4. Polyethylene glycol 5. Polyvinyl acetate 6. Polysaccharides (e.g., alginate) 7. Polyacrylates (e.g., Eudragit)

2. Pore forming agent: These pore forming agents can be incorporated into the semipermeablemembrane formulation in varying concentrations to control the size, density, and distribution of the pores, thereby influencing the drug release kinetics from the osmotic pump tablet. The selection of a specific pore forming agent depends on factors such as compatibility with other tablet components, desired release profile, and regulatory considerations.[5,6.]

Pore producing substances are employed in porosity control. osmotic pump tablets to create channels or pores within the semipermeable membrane, allowing for controlled drug release.[5,6.]

Table 3: Examples of pore forming agents

pore forming agents
1. Polyethylene glycol (PEG) 2. Sucrose 3. Sodium chloride 4. Dextran 5. Sorbitol 6. Mannitol 7. Polyvinyl alcohol (PVA) 8. Polyethylene oxide (PEO)

Osmotic agent: Typically present within the core tablet, this compound creates angradient of osmotic pressure across the semipermeable membrane, driving water influx into the tablet and promoting drug release.[5,6.]

Table 4: Examples of various osmogens with their osmotic pressure

Osmotic agent	Osmotic pressure (atm)
Lactose - fructose	500
Dextrose - fructose	450
Sucrose - fructose	430
Mannitol - fructose	415
NaCl	356
Fructose	335

3. **Coating:** Often applied to the outer surface of the semipermeable membrane, this layer provides additional protection and stability to the tablet. It may also include additives to modify the release characteristics or enhance patient compliance. These excipients are used to provide the necessary film-forming properties, mechanical strength, and stability to the coating layer. Additionally, plasticizers are often included to improve the flexibility and adherence of the coating, while opacifiers and pigments may be added for aesthetic purposes or to facilitate visual inspection of the tablets.[5,6.]

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Table 5: Examples of various excipients used in coating solution.

Excipients used in coating solution	
1.	Polyethylene glycol
2.	Polyvinyl acetate
3.	Polysaccharides (alginate)
4.	Polyacrylates (Eudragit)
5.	Plasticizers (triethyl citrate, dibutyl phthalate)

PRE – FORMULATION STUDIES

1. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy uses differences in absorbance band shapes and positions to identify specific functional groups in drugs and excipients. Individual and combined samples were completely pulverized using potassium bromide (1:100 ratio), pressed into clear pellets, and then scanned in an FTIR spectrophotometer between 4000 and 400^{cm-1} as a result, distinctive peaks for every sample and mixture could be obtained.[7]

2. Differential scanning calorimetry (DSC)

DSC is used to identify potential incompatibilities between drugs and excipients in dosage forms. It evaluates changes in melting endotherms, exotherms, and enthalpies of reaction. DSC was used to assess physical mixes of the medication and individual excipients at a 1:1 ratio. Precisely 5 mg of samples comprising individual components and mixtures were put into DSC pans, sealed to allow for efficient heat transfer, and heated at a rate of 20 °C per minute throughout a temperature range of 50-300°C. Thermograms were examined for signs of interactions, and thermograms from pure samples were compared to those from the improved formulation.[9]

3. Scanning Electron Microscopy (SEM)

SEM was employed to examine the surface-coated tablets both prior to and following the dissolution studies in order to investigate the drug release mechanism from them. Membranes were placed between wax paper sheets in a desiccator. and dried for 12 hours at 45°C before being analysed. Using a sputter coater, samples were vacuum-coated with gold. After being attached to brass stubs with double-sided tape. 20KV was used as the excitation voltage for the SEM scans, and the SEM system included an ion sputtering apparatus. Prior to and during dissolution, Surface morphology of the coated membrane of the best formulation film coating was evaluated, enabling a comparison of porous structures to appraise the potency of porogen and drug release capacities.[10]

PRE – COMPRESSION PARAMETERS

1) ANGLE OF REPOSE (θ)

The funnel method is used to determine the angle of repose (θ).A properly weighed powder mixture was placed in a funnel. Once the tip of the funnel struck the top of the powder pile, the height was adjusted.The blend was thenallowed to freely fall onto a surface, and the powder cone's diameter was measured. The following equation was used to calculate the angle of repose.[7,8,9]

$\tan \theta = 2h/d$

where , **θ** = angle of repose

h = heap height (cm)

d = circular support diameter (cm)

2) BULK DENSITY (e_b)

To determine bulk density, fill a graduated cylinder with granules and measure their bulk volume (Vb) and mass.The bulk density is then calculated using the following formula.[7,8,9]

Bulk density (e_b) = mass ofgranules (m) / bulk volume ofgranules (V_b)

3) TAPPED DENSITY (e_t)

A known quantity of granule blend is placed in a measuring cylinder and subjected to 1000 taps over a predetermined time. The resulting minimal volume occupied by the cylinder (V_t) and granule mass (m) are determined. The formula for determining tapped density (e_t) is:[7,8,9]

Tapped density (e_t) = mass of granules (m) / tapped volume of granules (V_t)

4) COMPRESSIBILTY INDEX (CARR'S INDEX)

Carr established the compressibility index (CI), which measures the Granular flow properties. It gives a clear evaluation of the compressibility of the granules, revealing their potential for

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powderstability and arching. Carr's index is calculated by applying the following formula:[7,8,9]

% Carr's index = $e_t - e_b / e_t \times 100$

Where, e_t = tapped density of granules
e_b = bulk density of granules

5) HAUSNER'S RATIO (H_R)

Hausner's ratio compares the tapped density with the bulk density to assess the granule flow properties.[7,8,9]

Hausner's ratio (H_R) = e_t / e_b

Where, e_t = granules tapped density
e_b =granules bulk density

Table 6: Different methods determine the level of flowability using different approaches

Flow characteristic	Angle of repose	Compressibility index	Hausner's ratio
Excellent	25-30	≤10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	More than 66	More than38	More than1.6

POST –COMPRESSION PARAMETERS

1. THICKNESS

i. CORE TABLET

Each tablet's thickness is measured using a vernier caliper (Mitutoyo Corp., Japan) giving precise millimeter measurements. Tablet thickness can have a maximum variation of ± 30%.[7,8]

ii. COATED TABLET

Following the dissolution process, the film was taken off the tablets and allowed to dry for an hour at 40°C. The Using electronic digital callipers (Mitutoyo Corp., Japan), thickness was measured, and mean values wererecorded.[7,8]

2. HARDNESS

Tablet hardness can be tested using a Monsanto hardness tester (Sisco, India) in kilograms per square centimeter (kg/cm²).[7,8,9]

3. FRIABILITY

Tablet friability testing was carried out utilizing a Friabilator Roche (Sisco, India). In the plastic chamber of the friabilator, twenty tablets with known weight (W0) were de-dusted, rotated for four minutes at a predefined speed of 25 rpm, and then weighed once more to ascertain weight. The following formula was used to estimate the percentage of friability.[7,8,9]

% Friability(F) = $(1- W/W_0) \times 100$

Where,W_0 = tablets weight before test after the test
W = tablets weight after the test

4. WEIGHT VARIATION TEST

In the weight variation test, each of the twenty tablets is weighed separately. Every tablet's weight is contrasted with the calculated average weight. Next, the computed % weight deviation is compared to the United States Pharmacopeia (USP) standards. To fail the USP test, a tablet can only depart from the specified % limit twice, and no more than two tablets can fall outside of it.[7,8,9]

Weight variation of n^{th} tablet = $(|\bar{w} - w_n|)/ \bar{w} \times 100$

Table 7: Specifications for weight variation in tablet

Average percentage of tablets	Maximum percentage difference allowed
130 (or) less	± 10
130 – 324	± 7.5
More than 324	± 5

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5. DRUG CONTENT UNIFORMITY TEST

Each batch of CPOP formulations had ten pills that were triturated to create powder. Using a magnetic stirrer, the powder equivalent of one tablet was dissolved over the course of 24 hours in a 100 ml volumetric flask filled with 0.1N HCl. After being suitably diluted, the solution was filtered through Whatman filter paper No. 1 and subjected to spectrophotometric analysis.[7,8,9]

6. DIAMETER OF TABLET

A vernier caliper (Mitutoyo Corp., Japan) is used to precisely measure the diameter of individual tablets in millimeters.[7,8]

7. IN VITRO DISSOLUTION STUDIES

Every one of the twenty tablets is weighed individually for the weight variation test. The weight of each tablet is compared to the computed average weight. The calculated percentage weight departure is then contrasted with USP (United States Pharmacopeia) guidelines. A tablet can only deviate from the designated percentage limit twice in order to fail the USP test, and no more than two tablets can do so.[7,8,9]

➢ **Mathematical modelling of in vitro drug release kinetics**

To ascertain the drug release kinetics of the porous osmotic pump tablet, the Higuchi, Korsmeyer, Peppa's, zero order, and first order equations were employed, along with the Hixson-Crowell equation.

a) Zero order model

➢ Drug release conforming to kinetics at zero order can be mathematically represented by the equation:[7,8,9.]

$$\mathbf{Q_t = Q_0 - K_0 t}$$

Where,Q_t= quantity of drug dissolved in t time
Q_0 = initial drug quantity in the solution
K_0= zero-orderrate constant.

➢ To study release kinetics, plot the cumulative quantity of drug release vs. time.

b) First order model

➢ The following equation describes the drug release with first order kinetics:[7,8,9]

$$\mathbf{LogC = Log\ C_0 – K_1 t / 2.303}$$

Where,C = quantity of drug yet to be released in time t
C_0 = initial drug concentration
K_1 = first order rate constant

➢ Plotting the logarithm of the cumulative proportion of medication remaining against timeallows for the analysis of the release kinetics.

c) Higuchi model

➢ According to Higuchi's classical diffusion equation, drug release from matrix devices is caused by a diffusion process.[7,8,9.]

$$\mathbf{Q = K_H \sqrt{t}}$$

Where,Q = amount of released drug in time t
K_H= Higuchi dissolution constant

➢ The cumulative drug release percentage can be plotted against the square root of time to determine release kinetics.

d) Korsmeyer-Peppas model (KP Model)

➢ For polymeric systems, Korsmeyer-Peppas devised a simple, semiempirical model that relates drug release to elapsed time exponentially.

➢ The expression for drug release in this model is as follows:[7,8,9.]

$$\mathbf{Log\ (M_t / M_\infty) = Log\ K + n\ Log\ t}$$

Where, M_t = amount of released drug at time t
M_∞=amount ofreleased drug after infinite time
K = release rate constant
n = release exponent for drug release mechanism

➢ The kinetics of release can be examined by plotting the logarithm of cumulative drug release percentage against the logarithm of time.

e) Hixson and Crowell model

➢ For drug powder with uniform particle size, Hixson and Crowell came up with an equation that states that the dissolving rate is proportional to the cube root of the particle volume.

➢ The following equation is used to express this:[7,8,9.]

$$\mathbf{W_0^{1/3} - W_t^{1/3} = \kappa\ t}$$

Where, W_0= initialquantity of drug in dosage form
W_t = drug quantity in dosage form at time t
κ= proportionality constant

➢ The kinetics of release can be investigated by graphing the cube root of the remaining drug percentage within the matrix against time.

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❖ **PATENTS ON CONTROLLED POROSITY OSMOTIC PUMP TABLETS**

Table 8: chronological patent listing

PATENT NO	TITLE	INVENTORS	YEAR	REF.NO
EP0169105	Controlled porosity osmotic pump	Zentner et al.	1986	[32]
US4886668	Multi- particulate controlled porosity osmotic pump	Haslam et al.	1989	[31]
EP0309051	Controlled porosity osmotic pump	Haslam et al.	1989	[30]
US4880631	Controlled porosity osmotic pump	John et al.	1989	[29]
ZA198807010	Controlled porosity osmotic pump	John et al.	1989	[28]
US4968507	Controlled porosity osmotic pump	Zentner et al.	1990	[27]
CA1266827A	Controlled porosity osmotic pump	Himmelstein et al.	1990	[26]
CA1320885C	Controlled porosity osmotic pump	Haslam et al.	1993	[25]
WO1994001093	Controlled porosity osmotic enalapril pump	Rork et al.	1994	[24]
EP1227800A1	Osmotic controlled release drug delivery device	Ruddy et al.	2001	[23]
WO2001032141A1	Osmotic controlled release drug delivery device	Ruddy et al.	2002	[22]
IN2004MU01385A20060721	Novel multiplying porous osmotic and diffusion drug delivery system	Rudresha et al.	2006	[21]
IN2005MU01282A20070302	Controlled porosity osmotic pump based drug delivery system	Chodankar et al.	2007	[20]
IN2005MU00321A 20070330	Novel multiplying porous osmotic and diffusion drug delivery system	Prasad et al.	2007	[19]
CN200810027661	Salvianolic acid controlled porosity osmotic pump tablets and method of preparing the same	Gao et al.	2008	[18]
WO2008052417	Controlled porosity osmotic pump tablets of high permeable drugs and the p[reparation method thereof	Wang et al.	2008	[17]
IN226882	Controlled porosity osmotic pump based	Roopali et al.	2008	[16]

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	drug delivery systems			
EP2085078	Controlled porosity osmotic pump tablets of high permeable drugs and the preparation method thereof	Wang et al.	2009	[15]
IN2007MU01469A 20090619	Novel swellable porous osmotic pump drug delivery	Pritam et al.	2009	[14]
US20100291208	Controlled porosity osmotic pump tablets of high permeable drugs and the preparation method thereof	Wang et al.	2010	[13]
CN101766581A 20100707	Porous controlled onset controlled release of diltiazem hydrochloride and its preparation method	Jiang et al.	2010	[12]
US2011084389	Surgery controlled release therapeutic device	Eric et al.	2011	[11]

II. CONCLUSION

The oral controlled porosity osmotic pump system controls the distribution of drugs that are poorly soluble in water. It consists of a core tablet encased in a semipermeable membrane containing pore-forming chemicals. Drug release is influenced by several factors, including drug category, solubility enhancer, membrane thickness, pore former concentration, and osmotic agent. Enhanced drug release is directly proportional to pore former, solubility enhancer, and osmotic agent concentrations, and inversely proportional to membrane thickness. Drug distribution is effectively controlled by this technique, which achieves zero-order release of the drug, independent of physiological factors.

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