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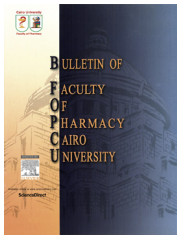

REVIEW ARTICLE

A review on controlled porosity osmotic pump tablets and its evaluation

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KEYWORDS

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Zero order

Abstract Conventional drug delivery system provides an immediate release of drug which does not control the release of the drug and does not maintain effective concentration at target site for a longer period of time. Hence to avoid the shortcomings there is development of various controlled drug delivery systems. Among these osmotic drug delivery system (ODDS) utilizes the principle of osmotic pressure and delivers drug dose in an optimized manner to maintain drug concentration within the therapeutic window and minimizes toxic effects. ODDS releases drug at a controlled rate that is independent of the pH and thermodynamics of dissolution medium. The release of drug from ODDS follows zero order kinetics. The release of drug from osmotic system depends upon various formulation factors such as solubility, osmotic pressure of the core components, size of the delivery orifice and nature of the rate controlling membrane. Controlled porosity osmotic pump (CPOP) contains drug, osmogens, excipients in core and a coating of semipermeable membrane with water soluble additives. In CPOP water soluble additives dissolve after coming in contact with water, resulting in an in situ formation of a microporous membrane. The present study gives an idea about osmosis, CPOP, components of CPOP and its evaluation.

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1. Introduction

Oral route[1] is a convenient route for the administration of various drugs because of low cost and ease of administration to the patients. But conventional drug delivery system does not control the release of drug and provides immediate release of drug. The rate and extent of drug absorption from conventional formulations change significantly depending on factors such as physicochemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of gastrointestinal (GI) tract, GI motility[2]and so on. To overcome these shortcomings researchers have focused on the development of novel drug delivery system[3] (NDDS). Among various designs of NDDS available in the market per oral controlled release system provides improved patient compliance, convenience and reduction in fluctuation in a steady state plasma level.[5] In Controlled drug delivery system (CDDS) there is a maximum utilization of drug optimizing reduction in total amount of dose and delivers short biological half life of drugs.[4] CDDS offers temporal and spatial control

Table 1 Osmotic agents with their osmotic pressure.[44–46]

S. No.	Osmogents	Osmotic pressure (atm)
1.	Adipic acid	8
2.	Fumaric acid	10
3.	Lactose	23
4.	Mannitol	38
5.	Potassium sulphate	39
6.	Tartaric acid	67
7.	Citric acid	69
8.	Dextrose	82
9.	Sorbitol	84
10.	Xylitol	104
11.	Potassium phosphate	105
12.	Melanic acid	117
13.	Sucrose	150
14.	Lactose-dextrose	225
15.	Potassium chloride	245
16.	Lactose-sucrose	250
17.	Fructose	355
18.	Mannitol-fructose	415
19.	Sucrose-fructose	430
20.	Dextrose-fructose	450
21.	Lactose-fructose	500
22.	Mannitol-dextrose	225
23.	Dextrose-sucrose	190
24.	Mannitol-sucrose	170
25.	Mannitol-lactose	130
26.	Sodium phosphate monobasic H_2O	28
27.	Sodium phosphate dibasic anhydride	29
28.	Sodium phosphate dibasic $7H_2O$	31
29.	Sodium phosphate dibasic $12H_2O$	31
30.	Sodium phosphate tribasic $12H_2O$	36

over the release of drug. But osmotic drug delivery system (ODDS) is one of the most advanced drug delivery systems that utilizes osmotic pressure as a driving force for controlled delivery of drugs. The release of drug from osmotic system is independent of presence and absence of food, pH of gastrointestinal (GI) tract, GI motility and hydrodynamic conditions of body due to rate controlling semi permeable membrane.[5] In ODDS the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window. ODDS delivers the drug at predetermined zero order rate for a prolonged time period. So it is used as the standard dosage form for constant drug delivery. ODDS provides a uniform concentration of drug at the site of absorption and thus after absorption allows maintenance of plasma concentration within therapeutic range which minimizes side effects and reduces the frequency of administration.[6] When an osmotic system comes in contact with water, water diffuses into the core through the micro porous membrane setting up an osmotic gradient and thereby controlling the release of the drug. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic devices.[7] Osmotic pressure is the pressure applied to the higher concentrated solution side to prevent transport[8] of water across the semi permeable membrane. The rate of drug delivery from osmotic system is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen. The ODDS has high in vitro-in vivo correlation. Hence osmotic drug delivery technique is most interesting and widely acceptable among all other techniques.[9] The following review concentrates on controlled porosity osmotic pump tablets of osmotic drug delivery systems.

Table 2 Criteria and specifications of controlled porosity osmotic pump.[35,67]

Criteria	Specifications
Plasticizer and flux regulating agent	0 to 50, generally 0.001 to 50 parts per 100 parts of wall material
Surfactants	0 to 40, generally 0.001 to 50 parts per 100 parts of wall material
Wall thickness	1 to 1000, generally 20 to 500 mm
Osmotic pressure	Generally between 8 to 500 atm
Core size	Between 0.05 mg to 5 g
Micro porous structure	5 to 95% pores between 10 mm to 100 mm diameter 0.1 to 60% generally 0.1 to 50% by weight based on total weight of excipients and polymer.

2. Osmotic drug delivery devices

Based on osmotic drug delivery devices[10,11] design and the state of use osmotic drug delivery system can be classified into the following categories (see Table 1).

2.1. Implantable osmotic pump

An implantable osmotic pump which delivers drug to a patient includes an osmotic engine, a substantially toroidal compartment disposed at least partially around the osmotic engine and a piston disposed within the compartment. The osmotic engine is employed to cause the piston to travel within the compartment and expel active ingredient contained within the compartment when the pump is implanted in an aqueous environment. Various types of implantable osmotic systems include the Rose and Nelson pump,[12] the Higuchi Theeuwes pump,[13] and the Higuchi Leeper pump[14] and implantable miniosmotic pump includes the Alzet[15] and Duros miniosmotic pump.[16]

2.2. Oral osmotic pump

Oral osmotic pump pertains to an osmotic device for delivering an active ingredient into the oral cavity of patients. The osmotic device comprises a shaped semi permeable membrane surrounding a compartment containing an active ingredient that is insoluble to very soluble in an aqueous fluid. The passage through the semi permeable membrane connects the exterior of the device with the compartment containing the active agent for delivering the agent from the device into the oral cavity. Based on the chamber the oral osmotic pump is classified into single chamber osmotic pump e.g. elementary osmotic pump[17] (EOP) and multi chamber osmotic pump such as push pull osmotic pump[18] (PPOP) and osmotic pump with nonexpanding second chamber.[19]

2.3. Specific types

Recent advances include various specific types of osmotic pump systems such as controlled porosity osmotic pump[20] (CPOP), osmotic bursting osmotic pump[21] (OBOP), Liquid OROS/Liquid oral osmotic system[22] e.g. L OROS hard cap, L OROS soft cap and delayed liquid bolus delivery system, telescopic capsule,[23] OROS CT,[24] sandwiched osmotic tablets[25] (SOTS), monolithic osmotic system,[26] osmat,[27] multi particulate delayed release systems[28] (MPDRS), pulsatile delivery based on expandable orifice,[29] pulsatile delivery by a series of stops[30]and lipid osmotic pump.[31]

3. Controlled porosity osmotic pump (CPOP)

Controlled porosity osmotic pump is an osmotic tablet in which membrane contains water soluble leachable pore forming agents. The coating of semi permeable membrane is done by a suitable coating method. The pump can be designed as single or multicompartment dosage form and the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure supported by a porous[32] substructure. The membrane is permeable to water but impermeable to solute. Water soluble pore forming additives are dispersed throughout wall of the membrane. CPOP lacks aperture to release the drugs, but drug release is achieved through the pores which are formed in the semi permeable wall in situ during the operation. When CPOP is exposed to water low levels of water soluble additives are leached from polymer materials that are permeable to water. The resulting sponge like structure is formed in the controlled porosity walls (see Table 2).

In this system the drug after dissolution inside the core is delivered from the osmotic pump tablet by hydrostatic pressure and diffusion through the pores incorporated in the micro porous semi permeable membrane and controlling the release of drug. The hydrostatic pressure is generated either by an osmotic agent[33] or by the drug itself or by a tablet component after water is imbibed across the semi permeable membrane. The rate of drug delivery depends upon factors such as water permeability of the semi permeable membrane, osmotic pressure of core formulation, thickness and total surface area of coating.[34] The designer can control all the factors and the formulation will not change in physiological conditions. The rate of flow of water into the device can be expressed as given below

$$dv/dt = Ak/h(d\pi - dp) \quad (1)$$

where dv/dt is rate of flow of water to the device, k and A are membrane permeability and surface area of membrane respectively, $d\pi$ and dp are osmotic pressure difference and hydrostatic difference between inside and outside of the membrane respectively.

4. Advantages of controlled porosity osmotic pump tablets[33,35]

(1) The release of drugs from controlled porosity osmotic pump tablets follows zero order kinetics after an initial lag.
(2) The delivery of drug may be delayed or pulsatile.
(3) The drug release is independent of physiological conditions of the body, gastric pH, and drug and of hydrodynamic condition.
(4) The drug delivery provides high degree of in vitro in vivo correlation.
(5) The drug release is higher than conventional drug delivery system.
(6) The release of drug is less affected by the presence of food in gastrointestinal tract.
(7) The delivery rate of drug from CPOP is predictable and programmable.
(8) There is no need of laser drilling because the holes are formed in situ.
(9) The production in scale up is very easy.
(10) The stomach irritation problems are reduced because the drug is delivered from the entire surface rather than single delivery orifice.
(11) It is useful for water soluble, partially water soluble and water insoluble drugs.

5. Disadvantages of controlled porosity osmotic pump tablets[35]

(1) The method of preparation is very costly.
(2) Retrieval therapy is not controllable in case of unexpected adverse effects.
(3) There is a chance of dose dumping if the coating process is not well controlled.
(4) There is a chance for the development of drug tolerance.

6. Drug release mechanism

When the controlled porosity osmotic pump tablets are in aqueous environment the water soluble additives get dissolved and form a micro porous structure in the coating membrane. The pores formed in SPM may be continuous with micro porous lamina, interconnected through tortuous paths of regular and irregular shapes.[36] Pore forming additives having a concentration range of 5%–95% produce pores with pore size ranging from 10Å to 100 μm. This technology is applicable for water soluble, partially water soluble and water insoluble drugs. The semi permeable membrane forms a sponge like structure when it is in contact with water. The water enters through pores of semi permeable membranes and forms a solution of drug which is released through pores. The rate of water inlet is depends on the type and concentration of osmogent and the drug release depends upon hydrostatic pressure created by inlet water, and the size and number of pores.[37]

Water is used as a solvent for different osmotic pump principles for drug delivery system. All pumps deliver the solvent flow across the semi permeable membrane for actuation. The solvent inflow through the membrane into the osmotic device dissolves the drug which is used as an osmotic agent and displaces the saturated drug solution through outlets. The volume flow of solvent into the core reservoir is expressed in Eq. (2).

$$\frac{dv}{dt} = \frac{A}{h}L(\sigma d\pi - dp) \quad (2)$$

where dv/dt is water flux, A is area of the semi permeable membrane, h is thickness of the membrane, $d\pi$ and dp are the osmotic and hydrostatic pressure difference between the inside and outside of the system, L is mechanical permeability and σ is the reflection coefficient. In case of an osmotic agent in a sealed

device a hydrostatic pressure equivalent to the osmotic pressure can build up over time. For drug release applications open release pore or multiple pores are essential which limit the hydrostatic pressure due to the continuous drug flow through the release pore or pores. As a result of which the hydrostatic pressure difference between the osmotic agent device and the outlet area is defined by the flow resistance of the release pore times the net flow of solvent across the semi permeable membrane. The effective drug release rate of the system through the orifice at a controlled rate is expressed in Eq. (3)

$$\frac{dm}{dt} = \frac{dv}{dt}C \tag{3}$$

where dm/dt is solute/drug delivery rate and C is the concentration of drug in dispersed fluid.

Reflection coefficient is taken to consideration when there is leakage of drug through the membrane. The SPM which is perfect does not allow solute to pass through it and σ is close to unity. If the orifice is sufficiently large the hydrostatic pressure will be negligible which tends to zero. Hence the Eq. (2) becomes

$$\frac{dv}{dt} = \frac{A}{h}L\sigma d\pi \tag{4}$$

The osmotic pressure of gastrointestinal fluids is negligible as compared to that of core, hence π is replaced by $d\pi$ and $L\sigma$ is replaced by a constant K. Hence the equation becomes

$$\frac{dv}{dt} = \frac{A}{h}K\pi \tag{5}$$

Hence the pumping drug rate from the core can be expressed as

$$\frac{dm}{dt} = \frac{A}{h}K\pi C \tag{6}$$

This fundamental equation[38] is applicable to all osmotically driven pumps as well as controlled porosity osmotic pump tablets.

7. Basic components of controlled porous osmotic pump tablets

7.1. Drugs

The drug which is water soluble in nature can be designed in this system only. The drugs having a short biological half life (2–6 h), prolonged treatment drugs e.g. nifedipine,[39] glipizide[40] etc. and highly potent drugs can be designed for this system.

7.2. Osmotic components/osmogents

Osmotic agents maintain a concentration gradient[41] across the membrane which is essential for designing osmotic formulations. During the penetration of biological fluid into the CPOP through semi permeable membrane, osmogens are dissolved in the biological fluid which builds up osmotic pressure inside the pump and pushes medicament outside the pump through delivery orifice. They create a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmogents[42] are used in the fabrication of osmotically controlled drug delivery systems and modified devices for controlled release of relatively poorly water insoluble drugs. Mostly polymeric osmogents are used for design of CPOP. Osmogents generate osmotic pressure in the concentrated solution ranging from 8 atm to 500 atm. These osmotic pressures can produce high water flows across the semi permeable membrane. The rate of water flow across the semi permeable membrane is given by Eq. (7).

$$dv/dt = AK\pi/h \tag{7}$$

where dv/dt is the rate of water flow across the membrane, A area of SPM, π is the osmotic pressure, K is the permeability and h is the thickness.

7.2.1. Classification of osmogents[43]

7.2.1.1. Water-soluble salts of inorganic acids osmogents. The examples of water soluble salts of inorganic acids osmogents are magnesium chloride or sulphate, sodium chloride, sodium sulphate, potassium chloride, sodium bicarbonate, sodium or potassium hydrogen phosphate etc.

7.2.1.2. Organic polymeric osmogents. The examples of organic polymeric osmogents are sodium carboxyl methylcellulose, hydroxyl propyl methyl cellulose, hydroxyl methylcellulose, methylcellulose, polyethylene oxide, polyvinyl pyrollidine, polyacrylamides, carbopols etc.

7.2.1.3. Carbohydrates. The examples of carbohydrates which are used for osmogents are arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose etc.

7.2.1.4. Water-soluble amino acids. The water soluble amino acids which are used for osmogents are glycine, leucine, alanine, méthionineds glycine, leucine, alanine, méthionine, etc.

7.2.1.5. Water soluble salts of organic acids osmogents. The water soluble salts of organic acids osmogents are sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate etc.

7.3. Semipermeable membrane (SPM)

Semi permeable membrane[44] is also known as selectively permeable membrane or partially permeable membrane or differentially permeable membrane.SPM is a membrane that allows solvent and certain molecules or ions to pass through it by diffusion or specialized facilitated diffusion. CPOP contains SPM as the outer layer. The membrane is impermeable to the passage of drug and other ingredients present in the compartments. The membrane is inert and maintains its dimensional integrity to provide a constant osmotic pressure during the drug delivery and is biocompatible with other ingredients of the formulation.[47] Cellulose acetate is mostly used for designing of various CPOP tablets. The formation of SPM includes cellulosic polymers such as cellulose ethers, cellulose esters and cellulose ester-ether. The cellulosic polymers have a degree of substitution of 0 to 3 on the anhydroglucose unit. The degree of substitution is the number of hydroxyl groups present on the anhydroglucose unit replaced by a substituting group. The examples of these groups include cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate etc. The other SPM forming polymers are group consisting of acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose dimethylamino acetate, polyamides, polyurethanes etc. The semi permeable membrane

is generally 200–300 μm thick to withstand the pressure within the device.

7.3.1. Ideal property of semi permeable membrane[48]

(1) The material must have sufficient wet strength and wet modulus.
(2) The semi permeable membrane must have rigid dimensional integrity during the operational time of the device.
(3) The membrane must have sufficient water permeability to retain water flux rate in the desired range.
(4) The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity.

7.4. Coating solvents

Coating solvents[21] are suitable for making polymeric solutions that are used for manufacturing the wall of osmotic device. It includes inert organic and inorganic solvents. The solvents used for coating solvents are methylene chloride, acetone, methanol, ethanol, isopropylalcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. The mixtures of solvents[49] include acetone-methanol(80:20), acetone-ethanol (80:20), acetone-water(90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water(75:22:3) etc.

7.5. Emulsifying agents

Emulsifying agents are added to wall forming material to produce an integral composition which is useful to make the wall of the device. They regulate the surface energy of materials to improve their blending[47] into the composite and maintain their integrity in the environment of use during the drug release period. The examples of emulsifying agents are polyoxyethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laureates, glycerol (sorbitan oleate, stearate or laurate) etc.

7.6. Flux regulating agents

Flux regulating or flux enhancing [50] or flux decreasing agents are used in wall forming materials to regulate the fluid permeability of flux through wall. This agent can be used to increase or decrease the liquid flux. The flux regulating agents may be hydrophilic substances and hydrophobic substances. The hydrophilic substances such as polyethylene glycols, polyhydric alcohols, polyalkylene glycols increase the flux whereas hydrophobic substances such as phthalates substituted with alkyl or alkoxy (diethyl phthalate or dimethoxyethyl phthalate) decrease the flux.

7.7. Wicking agents

Wicking agent has the ability to draw water into the porous network of delivery device. The wicking agent may be swellable or nonswellable in nature. It has the ability to undergo physisorption with water. Physisorption is the form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via vanderwaal's interactions between the surface of the wicking agent and the absorbed molecule. The wicking agent's function[51] is to carry water to the surfaces inside the core of the device and create channels or a network of increased surface area. The examples of wicking agents are colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, polyvinyl pyrrolidone, bentonite, sodium lauryl sulphate etc.

7.8. Plasticizers

Plasticizer is used to lower the temperature in phase transition of the wall and also increase the workability, flexibility and permeability of the fluids. The ranges of plasticizers or mixture of plasticizers are between 0.01 parts to 50 parts which are incorporated into 100 parts of wall forming materials.[52] Suitable solvents are used having high degree of solvent power for materials and compatible with the materials over both the processing and the temperature ranges to remain in the plasticized wall imparting flexibility to the material. The examples of plasticizers are phthalates (dibenzyl, dihexyl, butyl, octyl), triacetin,epoxidizedtallate,triisoctyltrimellitate,alkyladipates,citrates,acetates,propionates,glycolates,myristates,benzoates,halogenated phenyls etc.

7.9. Pore forming agents

The pore forming agents[53] form micro porous structure in the membrane due to their leaching during the operation of the system usually used for poorly water soluble drugs. The pores may be formed in the wall before operation of the system by gas formation by volatilization of components or by chemical reactions in polymer solution which creates pores in the wall. The pore formers may be inorganic and organic in nature.[54] The examples of pore forming are alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc, alkaline earth metals such as calcium chloride, calcium nitrate etc, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol, diols, polyols etc.

7.10. Barrier layer formers

The function of barrier former[55] is to restrict water entry into certain parts of the delivery system and to separate the drug layer from the osmotic layer. The examples of barrier layer formers are high density polyethylene, wax, rubber etc.

8. Specifications of controlled porosity osmotic pump

9. Compatibility studies

9.1. Fourier transform infrared spectroscopy (FTIR)

The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by

Table 3 Angle of repose and its observations.

Angle of repose (θ)	Observation
$<25°$	Free flowing granules
25–30°	Good flow
300-40°	Passable
$>40°$	Poorly flowing granules

analysing the significant changes in the shape and position of the absorbance bands. In this method individual samples[56] as well as the mixture of drug and excipients were ground and mixed thoroughly with potassium bromide (1:100) for 3–5 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm^{-1} in FTIR spectrophotometer. Then the characteristics peaks[57] of all samples as well as mixtures were obtained. Then the peaks of optimized[58] formulation were compared with pure drug and excipients. If there was no interaction between the peaks of drug and excipients of optimized formulation then it was said to be compatible.

9.2. Differential scanning calorimetry (DSC)

The compatibility of drug with the excipients used for formulation development was tested using differential scanning calorimetry.[58] Physical mixtures of drug and individual excipients in the ratio of 1:1 were taken and examined in DSC. Individual samples as well as physical mixture of drug and excipients were weighed to about 5 mg in DSC pan. The sample pan was crimped for effective heat conduction and scanned in the temperature range of 50–300 °C. Heating rate of 20 °C min^{-1} was used and the thermogram obtained was reviewed for evidence of any interactions. Then the themograms[59] were compared with pure samples versus optimized formulation.

10. Evaluation of osmotic pump tablets

10.1. Precompression parameters of osmotic pump tablets

10.1.1. Angle of repose (θ)

The angle of repose test is very sensitive to the method used to create the heap. Angle of repose may be determined by heap[60] shape measurement. By using the classical method angle of repose can be measured. The diameter of powder heap is measured and angle of repose is calculated using the following equation

$$\tan\theta = 2h/d \tag{8}$$

$$\theta = \tan^{-1}(2h/d) \tag{9}$$

where θ is the angle of repose, h is the height of heap in cm and d is the diameter of the circular support in cm. It is shown in Table 3. Angle of repose can be observed accurately by placing an initialization tube with an internal diameter equal to support diameter on the support. After manually filling the tube with the sample of powder the initialization tube goes up at a constant speed of 5 mm/s. As a result of which the powder flows from the tube to form a heap on the cylindrical support. This support rotates slowly around its axis. A CCD camera[61] takes pictures of the heap for different orientations. To get the results presented in the next Section 8 images separated by a rotation of 22.5° were recorded. In this way all the geometrical information was extracted. From each picture of the heap algorithm finds the position of interface powder/air by image analysis. The angle of repose (θ) is the angle of the isosceles triangle which has the same surface area as the heap. The isosceles triangle corresponds to the ideal heap shape.

Table 4 Relationship between powder flowability and % compressibility range.

% compressibility index	Flow type
5–15	Excellent flow (free flowing granules)
12–16	Good
18–21	Fair (powdered granules)
23–28	Poor (very fluid powders)
28–35	Poor (fluid cohesive powders)
35–38	Very poor (fluid cohesive powders)
>40	Extremely poor (cohesive powders)

Table 5 Hausner's ratio and its flow types.

Hausner's ratio	Flow type
1.2	Free flowing granules
>1.6	Poorly flowing granules

10.1.2. Bulk density (e_b)

Bulk density[62] is determined by pouring the granules into a graduated cylinder. The bulk volume (V_b) and mass (m) of the granules are determined. The bulk density is calculated by using the following formula.

$$\text{Bulk density } (e_b) = \text{Mass of granules } (m)/\text{Bulk volume of granules } (V_b) \tag{10}$$

10.1.3. Tapped density (e_t)

The measuring cylinder containing a known mass of granules blend is tapped 1000 times for a fixed time. The minimum volume occupied in the cylinder (V_t) and mass of the granules (m) are measured. The tapped density[63] is measured by using the following formula.

$$\text{Tapped density } (e_t) = \text{Mass of granules } (m)/\text{Tapped volume of granules } (V_b) \tag{11}$$

10.1.4. Compressibility index (Carr's index)

The compressibility index[64] determines the flow property characteristics of granules developed by Carr. The percentage compressibility of granules is a direct measure of the potential powder arch and stability. The Carr's index can be calculated by the following formula

$$\%\ \text{Carr's index} = \frac{e_t - e_b}{e_t} \times 100 \tag{12}$$

where e_t is the tapped density of granules and e_b is bulk density of granules. It is represented in Table 4.

Table 6 USP: specifications for weight variation of tablets.

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

10.1.5. Hausner's ratio

Hausner's ratio[59] is used for the determination of flow properties of granules. The ratio can be calculated by taking the ratio of tapped density to the ratio of bulk density. It is shown in Table 5.

10.2. Postcompression parameters of osmotic pump tablets

10.2.1. Thickness

The thickness[65] of individual tablets is measured by using vernier caliper which gives the accurate measurement of thickness. It provides information of variation of thickness between osmotic pump tablets. Generally the unit for thickness measurement is mm. The limit of the thickness deviation of each tablet is ±5%.

10.2.2. Hardness

The hardness[66] of tablets can be determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

10.2.3. Friability

Friability[67] of tablets was performed in a Roche friabilator. Ten tablets were initially weighed (W_0) together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the Plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed (W).The percentage of friability was calculated using the following equation

$$\%\ \text{Friability} = \text{F} = \left(1 - \frac{W_0}{W}\right) \times 100 \quad (13)$$

where, W_0 and W are the weight of the tablets before and after the test respectively. The limit for percentage of friability is between 0.5% and 1%.

10.2.4. Weight variation

The weight variation test[68] is done by weighing 20 tablets individually calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with USP specifications. The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. It is shown in Table 6.

$$\text{The weight variation of } n\text{th tablet} = \frac{(|\bar{w} - w_n|)}{\bar{w}} \times 100\% \quad (14)$$

where weight of tablets are w_1, w_2, w_3,...w_n..., w_{20}.and average weight of the tablets = $\bar{w}$

10.2.5. Disintegration test

In disintegration test[67] apparatus disintegration time of tablets is measured by placing tablets in each tube and the basket rack assembly is positioned in a 1-litre beaker of water or simulated gastric fluid or simulated intestinal fluid at 37 °C ± 2 °C such that the tablet remains 2.5 cm from the bottom of the beaker.

Table 7 Patents on controlled porosity osmotic pump tablets.

S. No.	Patent No.	Title	Publication date	Inventors	Ref. No.
1.	EP0169105	Controlled porosity osmotic pump	Jan.22,1986	Gaylen M Zentner, Gerald S Rork, Kenneth J Himmnelstein	73
2.	US5672167	Controlled release osmotic pump	Sept.30,1997	Amulya L Athayde, Rolf A Faste, C Russell Horres Jr, Thomas P Low	74
3.	WO1994001093	Controlled porosity osmotic enalpril pump	Jan.20,1994	John L Haslam, Gerald S Rork	75
4.	EP0309051	Controlled porosity osmotic pump	Mar.11,1992	John L Haslam, Gerald S Rork	76
5.	CA1320885	Controlled porosity osmotic pump	Aug.3,1993	John L Haslam, Gerald S Rork	77
6.	WO2001032149	Osmotic controlled release drug delivery device	May 10,2001	Laura A Debusi, Stephen B Ruddy, David E Storey	78
7.	US8109923	Osmotic pump with remotely controlled pressure generation	Feb.7,2012	LE Hood, MY Ishikawa, EKY Jung, R Langer, T Clarence, TLL Wood, VYH Wood	79
8.	US20100291208	Controlled porous osmotic pump tablets of high permeable drugs and the preparation process thereof	Nov.18,2010	Jingang Wang, Haisong Jiang	80
9.	WO2010081286	Timing controlled release porous tablet of diltiazem hydrochloride and the preparation method thereof.	Jul.22,2010	Haisong Jiang, Jingang Wang	81
10.	EP2085078	Controlled porosity osmotic pump tablets of high permeable drugs and preparation method thereof	Nov.20,2013	Jingang Wang, Haisong Jiang	82
11.	US5458887	Controlled release tablet formulation	Oct.17,1995	Chih Ming Chen, Charles SL Chiao, Jose Suarez	83
12.	US4687660	Pharmaceutical delivery system	Aug.18,1987	Richard W Baker, James W Brooke	84
13.	US4880631	Controlled porosity osmotic pump	Nov.14,1989	John L Haslam, Gerald S Rock	85
14.	US4968507	Controlled porosity osmotic pump	Nov.6,1990	Gaylen M Zentner, Gerald S Rork, Kenneth J Himmnelstein	86
15.	US4851228	Multiparticulate controlled porosity osmotic pump	Jul.25,1989	Gaylen M Zentner, Kenneth J Himmnelstein, Gerald S Rork	87
16.	US6753011	Combined diffusion/osmotic pumping drug delivery system	Jan.22,2004	Joaquina Faour	88

A standard motor moves the basket up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cpm (cycles per minute). USP disintegration test will be passed if all the tablets disintegrate and the particles are passed through the #10 mesh screen within the specified time.

10.2.6. Uniformity of drug content test

In this USP method 10 dosage units are individually assayed for their content according to the method described in the individual monograph. Unless otherwise stated in the monograph the requirements for content uniformity are met if the amount of active ingredient in each dosage unit lies within the range of 85–115% of the label claim and standard deviation is less than 6%.If one or more dosage units do not meet these criteria additional tests as prescribed in the USP are required.[69]

10.2.7. In vitro dissolution studies

In vitro dissolution[70] study is performed by using USP Type I Apparatus (Basket type). The tablet is kept in 900 ml of dissolution fluid phosphate buffer of pH 7.4 or 0.1 N HCl or simulated gastric fluid with a stirrer rotating at a specified r.p.m and maintaining the temperature at 37 ± 0.5 °C of dissolution media. 5 ml of samples withdrawn at different time intervals were replaced with fresh medium and analysed in UV–Visible spectrophotometer for estimation of absorbance taking a suitable blank solution. Finally the drug release rate is calculated using a suitable equation.

10.2.8. Scanning electron microscopy (SEM)

In order to observe the mechanism of drug release[71] from the developed formulations surface coated tablets before and after dissolution studies were examined using a scanning electron microscope. Membranes were dried at 45 °C for 12 h and stored between sheets of wax paper in a desiccator until examination. The samples (membranes) were fixed on a brass stub using a double sided tape and then gold coated in vacuum by a sputter coater. Scans were taken at an excitation voltage of 20KV in SEM fitted with ion sputtering device. The surface morphology[72] of coated membrane of optimized formulation film coating before and after dissolution was examined and by comparing the porous morphology the capability of porogen and drug release can be evaluated.

11. Patents on controlled porosity osmotic pump tablets

In recent years significant attention has been focused on the development of various types of osmotic drug delivery system. Currently many pharmaceutical companies have interest to patent osmotic drug delivery systems. Many patents have come under the name of controlled porosity osmotic pump. It is explained in Table 7.

12. Conclusion

Controlled porosity osmotic pump tablets utilize the principle of osmotic pressure for drug delivery system. The drug delivery from CPOP system is independent of the physiological factors of gastrointestinal tract. By optimizing various formulation factors such as solubility, osmotic pressure of core components and nature of rate controlling membrane the drug delivery can be controlled. The release of drug follows zero order kinetics and is safer than conventional dosage forms.

13. Conflict of interest

We declare that we have no conflict of interest.

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