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Review Article

A REVIEW ON CONTROLLED POROSITY OSMOTIC PUMP TABLETS AND ITS EVALUATION

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Abstract:
The objective of present review was to delivery of drugs in controlled pattern over a long period of time by the process of osmosis .Osmotic devices are the most promising strategy based systems for controlled drug delivery .They are the most reliable controlled drug delivery systems and could be utilized as oral drug delivery systems. The present review is concerned with the study of drug release systems which are tablets coated with walls of controlled porosity. When these systems are exposed to water, a low level of water soluble additive is leached from polymeric material. Semipermeable membrane and drug releases in a controlled manner over an extended period of time. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. In this paper, the basic components of controlled porosity osmotic pump tablets have been discussed briefly.
Keywords: Osmotic pump, controlled-porosity osmotic pump tablet, semipermeable membrane, osmogent.

Introduction:

Oral route 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[1,2] and so on. Drugs
can be delivered in a controlled pattern over a long pe riod of time by the process of osmosis. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form[3]The oral osmotic pump tablets have many advantages , such as reducing risk of adverse reactions , zero-order delivery rate, a high degree of invitro invivo correlation and improving patient compliance[4].CDDS offers temporal and spatial control over release of the 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]At the point when an osmotic system interacts with water, water diffuses into the core through the micro porous membrane setting up an osmotic gradient and in the manner controlling the release of the drug. Osmotic pressure created because of imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic devices.[6]

Osmotic pressure is the pressure applied to the higher concentrated solution side to forestall transport[7] of water across the semi permeable membrane. The rate of drug delivery from osmotic system is directly proportional to the osmotic pressure created because of imbibitions of fluids by osmogen. Hence osmotic

drug delivery technique is most intriguing and widely acceptable among all other techniques.[8] The following review concentrates on controlled porosity osmotic pump tablets of osmotic drug delivery systems

Table 1: Criteria and specifications of controlled porosity osmotic pump.[9,10]

Criteria	Specifications
Plasticizer and flux regulating agents	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 of wall materials
Core size	Between 0.05 mg to 5g
Osmotic pressure	Generally between 8 to 500 atm
Wall thickness	1 to 1000, generally 20 to 500 mm
Micro porous structure	5 to 95% pores between 10nm to 100nm diameter 0.1to 60% generally 0.1 to 50% by weight based on total weight of excipients and polymers.

Advantages

- Easy to formulate and simple in operations
- They typically provide Zero order release profile after an initial lag.
- Improve patients compliance with reduce dosage frequency.
- The release mechanisms are not dependent on drug
- Prolong therapeutic impact with uniform blood concentration
- Deliveries might be delayed or pulsed, if desired.
- Drug release is independent of gastric PH and Hydrodynamic condition.
- They are well characterized and perceived.
- A high level of in-vitro and in-vivo co relation (IVIVC) is obtained in Osmotic systems.
- The release rate of Osmotic systems is highly predictable and can be modified by modulating the release control parameters.
- The rationale for the approach is that the presence of water in GIT is generally constant, at least in terms amount required for enactment. and controlling osmotically base technologies.
- Higher release rates are possible for Osmotic systems compared with conventional diffusion controlled drug delivery systems.
- The release from Osmotic systems is minimally impacts by the presence of food in Gastrointestinal tract.

Disadvantages of controlled porosity osmotic pump tablets[12]

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

BASIC COMPONENTS OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS

1. **Drug:-** All drugs are not appropriate for CPOP as prolonged action medication. Drugs having following qualities are suitable for formulation of controlled porosity osmotic pump tablets:

- It should have short half – life
- Prolonged release of drug should be desired
- It should be potent in nature

- Solubility of drug should not be extremely high or very low.

Roger A. Rajewski *et al* (1999) studied the membrane controlling factors responsible for drug release from a controlled-porosity osmotic pump tablet (OPT) that utilizes sulfobutyl ether--cyclodextrin, (SBE)7m --CD, both as solubilizing agent and osmotic agent. The release rate of chlorpromazine (CLP) from OPTs containing (SBE)7m --CD increased with increasing amounts of micronized lactose and decreasing amounts of triethyl citrate. The effect of lactose particle size in the membrane on drug release was studied [13]

AK Philip et al (2008) developed an asymmetric membrane capsular system, formed in situ, for poorly water soluble drug, ketoprofen and evaluated it by both in vitro and in vivo methods for osmotic and controlled release of the drug. Membrane characterization by scanning electron microscopy showed an outer dense region with less pores and an inner porous region for the prepared asymmetric membrane.[14]

2. **Osmotic agent:** These are also known as osmogens or osmogents and are utilized to make osmotic pressure inside the system. At the point when the solubility of drug is low then the drug will show zero order release but at a slow rate. To enhance the release rate osmotic agent is added in the formulation. Osmotic agents maintain a concentration gradient across the membrane.They additionally create a driving force for the uptake of water and help in keeping up drug consistency in the hydrated formulation. Osmotic components are normally ionic compound comprising of either inorganic salts or hydrophilic polymer. Osmotic agents can be any salt like sodium chloride, potassium chloride or sulphates of sodium or potassium and lithium. Also sugars like glucose, sorbitol or sucrose or inorganic salts of carbohydrates can be osmotic agents. [15]

Specifications for core of controlled- porosity osmotic pump [16]

Property	Specifications
Osmotic pressure developed by a solution of core	8 to 500atm typically, with normally encountered water soluble drugs and excipient.
Core loading (size)	0.05 mg to 5 g or more (incorporate dosage forms for Humans and animals)
Core solubility	To get constant, uniform release of 90% or geater of the initially loaded core mass solubility, S, to the core mass mass density,, that is S/,should be 0.1 or lower Ordinary it happens when 10% of the initially core mass saturates a volume of external fluid equal to loaded the total volume of the initial core mass.

Classification of osmogents[17]

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.

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.

Carbohydrates:

The examples of carbohydrates which are used for osmogents are arabinose, ribose, xylose, glucose,

fructose, galactose, mannose, sucrose, maltose, lactose, raffinose etc.

Water-soluble amino acids: The water soluble amino acids which are used for osmogents are glycine, leucine, alanine, methionine's glycine, leucine, alanine, methionine, etc.

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.

OSMOGENS[18]

S.No.	Osmogen	Osmotic pressure (atm)
1	NaCl	356
2	Fructose	355
3	KCl	345
4	Tartaric acid	67
5	Citric acid	69
6	Dextrose	82
7	Sorbitol	84
8	Xylitol	104
9	Sucrose	150

COMBINED OSMOGEN[18]

S.No	Combined osmogen	Osmotic pressure (atm)
1	Lactose -Fructose	500
2	Mannose -Lactose	225
3	Lactose – Sucrose	250
4	Dextrose-Fructose	450
5	Sucrose -Fructose	430
6	Mannose-Fructose	415
7	Lactose-Dextrose	225

3. Semi permeable membrane (SPM)

An significant part of the CPOP is Semipermeable membrane housing. Therefore, the polymeric membrane choice is significant key to the osmotic delivery formulation. The membrane should posses certain attributes like impermeability to the passages of drug and other ingredients present in the compartments. The membrane should be dormant and keep up its dimensional integrity to provide a constant osmotic driving force during dug delivery. Any polymer that is permeable to water but impermeable to solute can be utilize as a coating material in osmotic devices. The semipermeable membrane must meet some performances.

Ideal properties of semi permeable membrane

- The membrane should be biocompatible.
- The material should have adequate wet strength and wet modulus.
- The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity.
- The membrane ought have adequate water permeability to retain water flux rate in the desired range .[19]

4. **Wicking Agents**.

It is characterized as the agent which is needed to bring the water inside the device. These agents enhance contact of water with the device. At the point when contact surface area is enhanced, more water enters. These have two types. They can be swellable or non-swellable. Solvent particles get attach with wicking agents by Van der Waals forces. This is

called physisorption. Wicking agents act as a mediators for water since they bring the water within of the device and because of which enhanced surface area produces.[20] **Examples are:** Colloidal silicon dioxide, PVP and Sodium lauryl sulfate.

5. Pore forming agents

These agents are especially utilized in the pumps created for poorly water soluble drug and in the development of controlled porosity or Multiparticulate osmotic pumps. The pore forming agents cause development of microporous membrane. The microporous wall may be formed in situ by a pore former by its leaching during the operation of the system. The pore forming agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent help to enhance the rate of drug released from the orifice of the drug. The examples are colloidal silicon dioxide. PVP, carbohydrates like sucrose, sorbitol and sodium lauryl sulphate[21].

6. Plasticizers

In Pharmaceutical coating, plasticizers or low molecular weight diluents are added to adjust the physical properties and improve film-forming characteristics of polymers. Plasticizers can change visco elastic behaviour of polymers fundamentally and these changes may influence the permeability of the polymeric films. Plasticizers can transform a hard and brittle polymer into a softener, more paliable material, and possibly make it more impervious to the mechanical stress. Plasticizers expands the workability, flexibility and permeability of coating solvents. PEG 600, PEG 200, ethylene glycol diacetate are used as plasticizers. Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulations of osmotic systems [22].

7. Coating solvents

Coating solvents[23] are suitable for making polymeric solution that are used for formulation 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[24] 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.

Specifications of controlled porosity osmotic pump

Compatibility studies

Fourier transform infrared spectroscopy (FTIR)

The utilization of FTIR technique permits pointing out the implication of the different functional groups of drug and excipients by Compatibility studies analysing the huge changes in the shape and position of the absorbance bands. In this method individual samples[25]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 in FTIR spectrophotometer. Then the characteristics peaks[26] of all samples as well as mixtures were obtained. Then the peaks of optimized[27] 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.

Differential scanning calorimetry (DSC)

The compatibility of drug with the excipients used for formulation development was tested using differential scanning calorimetry.[27] Physical mixtures of drug and individual excipients in the ratio of 1:1 were taken and examined in differential scanning calorimetry. 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[28] were compared with pure samples versus optimized formulation.

Evaluation of osmotic pump tablets

Precompression parameters of osmotic pump tablets

- **Bulk Density[29]**

The bulk density by using the following formula

Bulk density = Weight of granules/ Bulk volume of granules

- **Tapped Density**[30]

The tapped density is measured by using the following formula

Tapped density = Weight of granules/ Tapped volume

- **Carr's compressibility index**[31]

The Carr's index can be calculated by the following formula

Compressibility index = Tapped density-bulk density/Tapped density ×100

- **Hausner's ratio**[28] The ratio can be calculated by taking ratio of tapped density to the ratio of bulk density

Hausner's ratio = Tapped density/Bulk density

- **Angle of repose (h)**

The angle of repose test is very sensitive to the method used to create the heap. Angle of repose may be determined by heap 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.

$$\tan \theta = 2h/d$$

$$\theta = tan^{-1}$$

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.

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)

Evaluation uncoated/core tablet.

Hardness

Although hardness test is not an official, tablet should have sufficient handling during packing and transportation. Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying the force. The hardness of 3 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in Kg/cm2

Weight Variation Test

20 tablets were weighed individually, average weight was calculated and individual tablet weight was compared to the average USP weight variation test.

Friability

Friability test was performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche Friabilator was used for the purpose. Compressed tablets should not more than 1% of their weigh[33] .The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo= Initial weight of tablet

W= weight of tablets after revolution

Thickness

The thickness of the tablet was measured using Vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.[33]

In-vitro Dissolution Study of Coated Tablet

The *In-vitro* dissolution test for press coated tablets were performed in triplicate using an eight-station USP type Π (paddle) apparatus at 37°C ± 0.5°C and 50 rpm speed in 500 ml each pH 6.8 phosphate buffer for rest of time were used as dissolution media. Aliquots of 5 ml dissolution fluid were removed at specified time intervals of one hour and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots were filtered through Whatman filter paper, suitably diluted using dissolution medium and analyzed for the amount of drug released by a spectrophotometer at a required wavelength respectively. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from reference standard. Cumulative percentage drug release was calculated.[34]

Kinetics of drug release

Zero-order model

If drug release from controlled release formulation is stable in fluid at the absorption site, has similar absorption sites and it absorbed rapidly and completely after its release then, its rate of appearance in plasma will be governed by its rate of release from the controlled release formulation. Thus, when the drug release follows zero-order kinetics, absorption will also be a zero-order process and concentration of drug in plasma at any given time can be given by equation [35]

$$C = F K_o (1-e^{-ket}) / K_E V_d$$

Patents on cotrolled porosity osmotic pump tablets

Sr. No.	Title	Patent No.	Publication date
1.	Controlled porosity osmotic pump[36]	EP0169105	01-22-1996
2.	Controlled release osmotic pump	US5672167	09-30-1997
3.	Controlled porosity osmotic enalpril pump[37]	WO1994001093	01-20-1994
4.	Controlled porosity osmotic pump[38]	EP0309051	03-11-1992
5.	Controlled porosity osmotic pump[39]	CA1320885	08-03-1993
6.	Osmotic controlled release drug delivery device[40]	WO2001032149	05-10-2001
7.	Osmotic pump with remotely controlled pressure generation[41]	US8109923	02-07-2012
8.	Controlled porous osmotic pump tablets of high permeable drugs and the preparation process thereof. [42]	US20100291208	11,18,2010
9.	Timing controlled release porous tablet of diltiazem hydrochloride and the preparation method thereof .[43]	WO2010081286	07-22-2010
10.	Controlled porosity osmotic pump tablets of high permeable drugs and preparation method theeof. [44]	EP2085078	11-20-2013
11.	Controlled release tablet formulation[45]	US5458887	10-17-1995
12.	Pharmaceutical delivery system46	US4687660	08-18-1987
13.	Controlled porosity osmotic pump[47]	US4880631	11-14-1989
14.	Controlled porosity osmotic pump[48]	US4968507	11-06-1990
15.	Multi particulate controlled porosity osmotic Pump[49]	US4851228	07-25-1989
16.	Combined diffusion/osmotic pumping drug delivery system[50]	US6753011	01-22-2004

Conclusion

Osmotic drug delivery systems are new methodology for a controlled delivery of dosage form. The release mechanisms are not dependent on drug.Prolong therapeutic impact with uniform blood concentration. Controlled porosity osmotic pump tablets utilize the principle of osmotic pressure for drug delivery system. 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.

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